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FINAL

DRINKING WATER CRITERIA DOCUMENT

FOR

ANTIMONY

Health and Ecological Criteria Division
Office of Science and Technology
Office of Water
U.S. Environmental Protection Agency
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FOREWORD

Section 1412 (b)(3)(A) of the Safe Drinking Water Act, as amended in 1986, requires the Administrator of the Environmental Protection Agency to publish Maximum Contaminant Level Goals (MCLGs) and promulgate National Primary Drinking Water Regulations for each contaminant, which, in the judgment of the Administrator, may have an adverse effect on public health and which is known or anticipated to occur in public water systems. The MCLG is nonenforceable and is set at a level at which no known or anticipated adverse health effects in humans occur and which allows for an adequate margin of safety. Factors considered in setting the MCLG include health effects data and sources of exposure other than drinking water.

This document provides the health effects basis to be considered in establishing the MCLG. To achieve this objective, data on pharmacokinetics, human exposure, acute and chronic toxicity to animals and humans, epidemiology, and mechanisms of toxicity were evaluated. Specific emphasis is placed on literature data providing dose-response information. Thus, while the literature search and evaluation performed in support of this document was comprehensive, only the reports considered most pertinent in the derivation of the MCLG are cited in the document. The comprehensive literature data base in support of this document includes information published up to April 1987; however, more recent data have been added during the review process and in response to public comments.

When adequate health effects data exist, Health Advisory values for less-than-lifetime exposures (One-day, Ten-day, and Longer-term, approximately 10% of an individual's lifetime) are included in this document. These values are not used in setting the MCLG, but serve as informal guidance to municipalities and other organizations when emergency spills or contamination situations occur.

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I. SUMMARY

Antimony (Sb) is a semimetal element of Group V, sharing some chemical properties with lead, arsenic, and bismuth. The most stable valence states of antimony are Sb^{3+} and Sb^{5+}. Numerous inorganic and organic compounds of antimony are known. Most of the common antimony compounds are slightly to readily soluble in water.

About 7 to 15% of an oral dose of trivalent antimony is absorbed by rodents. No estimate of gastrointestinal absorption in humans was located in the available literature. Absorbed antimony usually distributes to most tissues of the body, with some preferential accumulation in bone, thyroid, and adrenal. In mice injected intramuscularly with either antimony dextran glucoside or N-methyl-glucamine antimonate, the compounds were absorbed from the site of injection and deposited in the liver and spleen. Trivalent antimony is readily taken up by red blood cells, but pentavalent antimony does not enter red blood cells.

Claims have been made that Sb(V) is reduced to Sb(III) in the body, but no strong evidence exists to support this idea. Pentavalent antimony is excreted primarily in the urine of most species, including humans. In the mouse, white rat, hamster, guinea pig, rabbit, dog, and human, trivalent antimony is excreted in both the urine and feces, the ratio depending upon the species. In cows, 82% of the total dose was excreted in the feces, 1.1% in the urine, and 0.008% in the milk when $^{124}SbCl_3$ was administered orally. When $^{124}SbCl_3$ was given intravenously to cows, 2.4% of the total dose was excreted in the feces, 51% in the urine, and 0.08% in the milk.

Antimony shows little tendency to accumulate in the body. Levels of antimony have been reported in human milk and tissue. A mean of 3 ng Sb/g of milk was reported in Italian women. A mean concentration of 17.51×10^{-8} g/g dry weight of 90 pineal glands was reported in humans for both sexes. A median concentration of 0.015 ppm was found in the bone tissue of industrially exposed workers, whereas only 0.007 ppm was found in the control group. In mice fed $^{125}SbCl_3$ in the diet, a steady-state whole-body level was reached after 4 days. Following intraperitoneal injection in mice, antimony was cleared from the body biphasically, with a rapid phase ($t_{1/2}$ = 6 hours) accounting for about 95% of the dose and a slow phase ($t_{1/2}$ = 2.4 days) accounting for 5% of the dose. In mice fed antimony in the diet during pregnancy and 15 days postpartum, antimony was cleared biphasically, with half-times of 1.8 and 96 days when exposure was discontinued. In mice exposed to 0.8 mg Sb/kg/day for life (mean $\pm$ SE was 786 $\pm$ 3.7 days for males and 843 $\pm$ 47.8 days for females), tissue levels of antimony at time of natural death were only 6 to 14 ug Sb/g tissue. Similar results were obtained in rats exposed to 0.4 mg Sb/kg/day for life (mean $\pm$ SE was 999 $\pm$ 78 days for males and 1,092 $\pm$ 30.0 days for females), although levels tended to increase somewhat with age at time of natural death ($p < 0.05$).

Estimates of acute oral LD_{50} values in mice and rats range from 115 to 600 mg Sb/kg. An oral LD_{50} of 15 mg/kg has been reported in rabbits. Intravenous and intraperitoneal LD_{50} values range from 11 to 329 mg Sb/kg.

Early acute oral toxicity studies showed that considerable variation in sensitivity to antimony exists among species; mice and rats are less sensitive than dogs and cats. In addition, considerable variation in toxicity exists between different chemical forms of antimony; the soluble compounds, especially potassium antimony tartrate, are more toxic than the less soluble oxides.

The most prominent signs of acute oral antimony toxicity are nausea and vomiting, often with diarrhea. In dogs and cats, the emetic dose of potassium antimony tartrate (in water) is about 12 and 4.2 mg Sb/kg, respectively. In one study (Flury, 1927), exposure of rats and mice to high doses of insoluble antimony compounds (e.g., Sb_2O_3, Sb_2O_5) was without effect. However, in another study (Potkonjak and Vishnjick, 1983), intraperitoneal or endotracheal administration of Sb_2O_3 and Sb_2O_5 suspension (50 mg of dust) caused pneumoconiosis in rats. In yet another study (Pribyl, 1927), lower doses of potassium antimony tartrate (5.6 mg Sb/kg/day, given in milk for 1 to 3 weeks) caused only minor changes in blood and urine nitrogen levels in rabbits but produced histological changes in the intestine, liver, and kidney.

Parenteral administration of antimony (as potassium antimony tartrate) at doses of 1.5 to 15 mg Sb/kg results in various signs of myocardial injury. One report of injury to the inner ear of guinea pigs has been reported following repeated injections with sodium antimony bis(pyrocatechol-2,4-disulfate) and piperazine-di-antimonyl tartrate.

Lifetime oral exposure to potassium antimony tartrate (about 0.8 mg Sb/kg/day) in drinking water was without effect in mice, but 0.4 mg Sb/kg/day in drinking water caused decreased longevity and altered blood levels of cholesterol and glucose in rats. Doses of 8 to 100 mg Sb/kg/day administered in water or feed (as potassium antimony tartrate) for 4 months to 1 year did not cause decreased growth in rats or rabbits, but histological changes were observed in tissues.

Parenterally administered antimony (about 2.2 mg Sb/kg) led to decreased fertility in rabbits. No abnormalities were found in rat fetuses whose mothers

were exposed to the pentavalent antimony drug RL-712. No adverse effects were found in ewes whose mothers were fed potassium antimony tartrate for 45 days or throughout gestation.

Sodium antimony tartrate has been found to be mutagenic in bacteria, rat bone marrow cells, and human lymphocytes. Lifetime exposure of rats and mice to potassium antimony tartrate (in water) at doses of 0.4 to 0.8 mg Sb/kg/day did not result in any increase in tumor frequency.

Few studies were found of antimony toxicity following oral exposure in humans. Most cases involved ingestion of food or liquid stored in antimony-containing enamel vessels, and the symptoms that followed were characteristic of gastrointestinal distress (nausea, vomiting). In one case, administration of 132 to 198 mg antimony led to severe vomiting, diarrhea, and finally death.

Inhalation of antimony under industrial settings is more common, and abnormal electrocardiograms (EKGs) and increased ulcer frequency have been related to antimony exposure. Parenteral administration of antimony compounds is used in the treatment of various parasitic diseases. Adverse effects of such treatment have included vomiting, diarrhea, liver dysfunction, and skin abnormalities.

Dose-related increases in EKG abnormalities were found in 59 Kenyan patients following 65 courses of antimony treatment. An increase in lung tissue concentration of antimony (280 ppb ug/kg compared with 32 and 19 ppb in controls) was found in 76 copper smelter workers at autopsy. Suggestive evidence of adverse effects (spontaneous abortions, premature births, etc.) of antimony was presented in female workers employed in an antimony plant.

Antimony is thought to exert its toxic effects by interacting with intracellular enzymes or cofactors. A number of sulfhydryl-containing compounds reduce the toxic effects of antimony, suggesting that it may bind to cellular sulfhydryl groups. Antimony has been reported to increase the activity of heme oxygenase, to increase the action of thyroid hormone, and to decrease the toxicity of selenium, but the mechanisms of these effects are not known.

There were no suitable studies to calculate the one-day or ten-day health advisories for a 10-kg child. It was, therefore, recommended that the Drinking Water Equivalent Level (DWEL) of 15 ug/L be used as a conservative estimate for the one-day and ten-day health advisories. Similarly, a suitable study for the calculation of a Longer-term HA was not available. Therefore, it is recommended that the Drinking Water Equivalent Level (DWEL) of 15 ug/L be taken as an appropriate estimate of the Longer-term HA value. A LOAEL of 0.43 mg/kg/day, based on decreased longevity in a lifetime study in rats supplied potassium antimony tartrate in water, was used to calculate a Reference Dose (RfD) of 0.4 ug/kg/day and a DWEL of 15 ug/L (15 ug/L). A limit of 50 ug/L is recommended in the U.S.S.R.

Antimony has been found to be mutagenic in several test systems, and various types of tumors, including lung neoplasms, have been induced in rats upon inhalation exposure; however, no evidence has been found that orally ingested antimony is carcinogenic. No subpopulation has been identified that is more sensitive to the effects of antimony than is the general population.

II. PHYSICAL AND CHEMICAL PROPERTIES

Antimony is a semimetal element with atomic number 51 and an atomic weight of 121.75. It occurs in four valence states (0, 3-, 3+, and 5+) and forms a large number of organic and inorganic compounds. Table II-1 lists the important properties of antimony and some common antimony compounds.

Antimony has been used by man since early times. Ancient Chinese literature suggests that its use was known some 5,000 years ago (Dyson, 1928). Antimony (or stibium, as designated by the ancient Latins) is not an abundant mineral but is a component of many ores, of which antimony trisulfide (stibnite) is the most abundant (Weast et al., 1986). Antimony is used in modern industry as an alloy in semiconductor technology, batteries, antifriction compounds, ammunition, cable sheathing, flame-proofing compounds, ceramics, glass, and pottery. In 1979, U.S. production of antimony was reported to be approximately 35,000 metric tons per year (CEH, 1985). The most widely known and earliest pharmaceutical antimony compound is tartar emetic (potassium antimony tartrate). A number of organic antimony compounds have been developed in recent times that are safer and more effective than tartar emetic.

Table II-1. Physical Properties of Antimony and Some Antimony Compounds

Chemical	Synonyms	Formula	Molecular weight	Valence state	Solubility[a] in water (g/100 g)
Antimony	Stibium	Sb	121.75	0	vss
Potassium antimony tartrate	Tartar emetic	$KSbOC_4H_4O_6$	324.92	+3	8.3
Sodium antimony tartrate	Stibunal, Emeto-Na	$NaSbOC_4H_4O_6$	308.83	+3	66.7
Antimony sulfate	--	$Sb_2(SO_4)_3$	531.72	+3	i
Antimony trichloride	--	$SbCl_3$	228.12	+3	601
Antimony trifluoride	--	SbF_3	178.76	+3	387.4
Antimony trioxide	--	Sb_2O_3	291.52	+3	ss
Antimony pentoxide	--	Sb_2O_5	323.52	+5	ss
Antimony tartrate	--	$Sb_2(C_4H_4O_6)_3 \cdot 6H_2O$	795.81	+3	s
Sodium antimony bis(pyro-catechol-2,4-disulfate)	Stibophen NF	$C_{12}H_{18}Na_5O_{23}S_4Sb$	895.21	+5	s

[a]Abbreviations used:
vss = very slightly soluble.
i = insoluble.
ss = slightly soluble.
s = soluble.

SOURCE: Adapted from Weast et al. (1986) and Windholz et al. (1983).

III. TOXICOKINETICS

A. ABSORPTION

Moskalev (1959) dosed white rats (mean body weight 165 g, strain not specified) with potassium antimony tartrate (4.4 mg/kg) via gastric gavage or intravenous (iv) injection. The dose included 7 ug of ^{125}Sb. The animals were sacrificed at definite intervals after antimony administration. Organ samples, including urine, feces, and blood, were assayed for 125Sb activity. Results were reported as a percentage of the administered radioactivity per gram wet weight of tissue and entire organ. Roughly 15% of the radioactive dose was absorbed from the intestine.

Gerber et al. (1982) studied the absorption of tracer levels of ^{125}Sb (given as $^{125}SbCl_3$ in food) in pregnant BALB/c mice following repeated dosing. Total-body radioactivity reached an equilibrium level (1.7% of the daily intake) within 4 days. Assuming a half-life of 6 hours (see Section III.E, Bioaccumulation and Retention), the authors calculated that 7% of the ingested $SbCl_3$ was absorbed.

Combined elimination data from cows administered single oral or intravenous doses of $^{124}SbCl_3$ (see Section III.D, Excretion) indicated that very little (<5%) of the orally administered dose was absorbed via the gastrointestinal tract of ruminants. Most of the administered radiolabel was excreted in the feces (Van Bruwaene et al., 1982).

Felicetti et al. (1974) studied the retention of oral doses of trivalent or pentavalent 124Sb-tartrate (specific activities not reported) in Syrian hamsters. An oral dose of 2 uCi/mL was given via gastric gavage. Two hamsters were given 2 mL, two were given 1 mL of trivalent 124Sb-tartrate, and four

were given 1 mL of pentavalent 124Sb-tartrate. Very little of either the trivalent or pentavalent antimony was absorbed (no data given). For both valence states, antimony was retained (in the body) with a half-life of less than 1 day. The two animals that received 2 mL of the trivalent compound retained 9 and 15% of the dose by day 4, most of which (88 to 90%) was found in the gastrointestinal tract. In the other four animals, 1.6 to 2% of the dose was retained on day 4; of this, 61 to 64% was in the gastrointestinal tract.

B. DISTRIBUTION

Gerber et al. (1982) studied distribution of tracer levels of $^{125}SbCl_3$ given in food to pregnant BALB/c mice. The diet containing ^{125}Sb was started on the day the vaginal plug was observed. After 6 days, animals were sacrificed, and tissue levels of ^{125}Sb were measured. Concentrations (expressed as percent daily dose per gram tissue) in lung, bone, ovary, and uterus ranged from 0.085 to 0.2%, although the results were judged by the authors to be somewhat unreliable (due to low levels of radioactivity). From 30 to 36% of the daily dose (assuming 3 g of food was ingested daily) was found in the intestinal tract.

Westrick (1953) studied antimony distribution in rats. Groups of five male Sprague-Dawley rats (average weight about 120 g) were fed diets containing 0 or 2% Sb_2O_3 for 7 weeks. Using a mean body weight of 0.18 kg (the mean of reported initial and final weights) and assuming average food consumption of 12 g/day (Arrington, 1972), this corresponds to an average daily dose of about 1,100 mg Sb/kg/day. After 49 days, animals were sacrificed, and tissue levels of antimony were measured. Average concentrations in the liver, kidney, heart, spleen, lung, adrenal, and thyroid were 8.9, 6.7, 7.6, 18.9, 14, 67.8, and 88.9 ug Sb/g tissue, respectively. A wide variation was observed within the sample

values of some tissues; for example, ^{125}Sb concentrations in the thyroid ranged from 10.7 to 280 ug/g tissue. A similar pattern of antimony distribution was found in tissues of two adult male rabbits dosed by capsule with 13 mg Sb_2O_3/kg/day (10.9 mg Sb/kg/day) for 20 days.

Gerber et al. (1982) also measured tissue distribution in pregnant BALB/c mice following intraperitoneal (ip) injection of $^{125}SbCl_3$ at day 12 of pregnancy. Peak concentrations in tissues (percent dose per gram tissue) were observed at 2 to 6 hours after injection. Highest levels (approximately 50%) were seen in the intestine and bone surfaces. Levels in other tissues observed at 2 hours were 1 to 5% in the uterus and ovary, and 0.01 to 1.0% in the kidney, liver, spleen, lung, thyroid, blood, muscle, skin, and brain. Low levels (about 0.1%) were measured in the placenta and fetus.

Casals (1972) investigated the absorption and tissue distribution of antimony in NMRI mice. Female mice were injected intramuscularly (im) either with antimony dextran glucoside (RL-712) (52 mg Sb/kg) or with N-methyl-glucamine-antimonate (glucantime) (50.3 mg Sb/kg), and sacrificed at various intervals between 6 hours and 6 weeks after the injection. RL-712 was absorbed from the site of injection and deposited mainly in the liver and spleen (Table III-1). Glucantime was also deposited in liver and spleen but in smaller amounts (Table III-2).

Rowland (1971) studied distribution of antimony in humans given a single iv injection of ^{124}Sb-labeled potassium antimony tartrate. Four main compartments were determined via surface scanning: blood, liver, skeletal tissue, and urine. A detailed model of the distribution in humans is shown in Figure III-1.

Table III-1. Antimony Levels in Tissue or Organs of Mice Administered 52 mg Sb/kg Body Weight as RL-712[a]

Time after injection	Skeletal muscle	Kidneys	Heart	Spleen	Liver
6 hours	1.3	15.3	24.4	65.1	156.8
24 hours	17.6	14.3	26.0	67.6	--
48 hours	33.8	11.7	23.5	39.7	124.0
72 hours	--	13.6	22.2	--	105.0
1 week	--	12.7	21.1	32.7	80.6
2 weeks	--	9.1	8.8	7.4	68.0
3 weeks	--	4.4	6.8	7.5	66.7
4 weeks	--	0.5	1.3	6.6	33.6
5 weeks	--	1.0	2.0	5.0	34.0
6 weeks	--	1.4	1.5	4.6	20.7

[a]Expressed in ug of antimony per g wet tissue (organ).

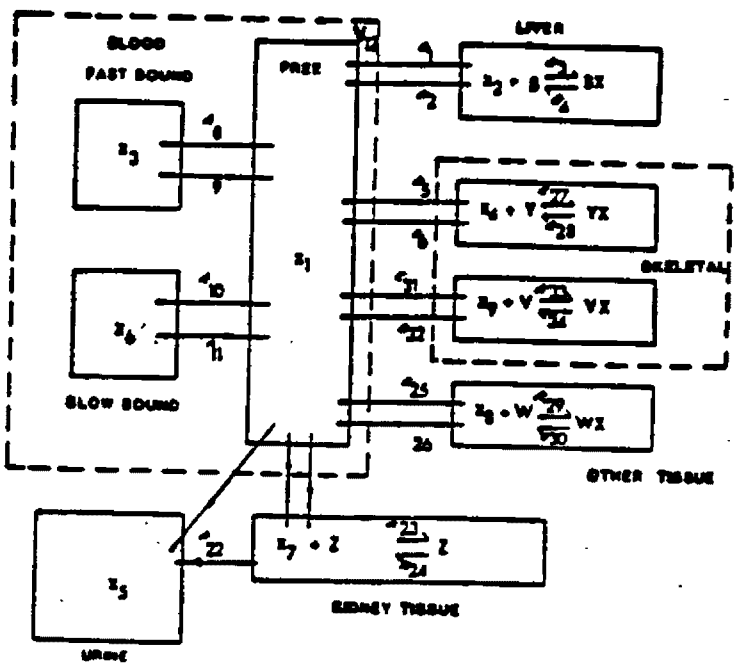
SOURCE: Adapted from Casals (1972).

Table III-2. Antimony Levels in Tissue or Organs of Mice Administered 50.3 mg Sb/kg Body Weight as Glucantime[a]

Time after injection	Skeletal muscle	Kidneys	Heart	Spleen	Liver
24 hours	1.0	3.5	4.5	4.5	7.5
1 week	--	2.5	2.0	2.5	7.5
4 weeks	--	$\leq$0.5	$\leq$0.5	$\leq$0.5	3.0

[a]Expressed in ug of antimony per g wet tissue (organ).

SOURCE: Adapted from Casals (1972).



Definition of the Variables

X_1	Concentration of:	free exchangeable antimony in blood
X_2		free exchangeable antimony in liver
X_3		antimony in "fast bound" blood compartment
X_4		free exchangeable antimony in skeletal A
X_5		antimony in urine
X_6		antimony in "slow bound" blood compartment
X_7		free exchangeable antimony in kidney tissue
X_8		free exchangeable antimony in "other" tissue
X_9		free exchangeable antimony in skeletal B
B		binding substance in liver
Y		binding substance in skeletal A
V		binding substance in skeletal B
W		binding substance in "other" tissue
Z		binding substance in kidney tissue
BX		bound complex in liver
YX		bound complex in skeletal A
VX		bound complex in skeletal B
WX		bound complex in "other" tissue
ZX		bound complex in kidney tissue

Figure III-1. Mathematical model for the distribution of antimony in humans.

SOURCE: Adapted from Rowland (1971).

Leffler and Nordstroem (1983) demonstrated the transfer of Sb from maternal to fetal blood in three Syrian golden hamsters intratracheally exposed to antimony on days 13 and 15 after fecundation. Experimental details were not given.

Molokhia and Smith (1969) incubated antimony (trivalent or pentavalent) compounds with equine whole blood in vitro and found that the erythrocyte membrane was permeable to trivalent antimony and impermeable to pentavalent antimony. Trivalent antimony bound to plasma proteins but not to erythrocytes.

Otto et al. (1947) studied antimony distribution between blood cells and plasma in humans. Fourteen adult black males with filiaria were treated for 5 days by daily im injection: six were administered lithium antimony thiomalate (anthiomaline) (up to 21 daily doses of 0.5 mg Sb(III)/kg); three were administered monosodium antimony thioglycollate (M.A.T.) (up to 11 daily doses of 0.5 mg Sb(III)/kg); two were administered iv injection twice daily of neostibosan (2 to 4 mg Sb(V)/kg/dose); and three were administered iv injection twice daily of stibanose (solustibosan) to 6 mg Sb(V)/kg/dose). Antimony concentrations in red blood cells and plasma were measured colorimetrically (Table III-3). For both trivalent and pentavalent antimony, plasma concentrations were sustained for only a short time (well under 24 hours). For both trivalent compounds, antimony was found largely inside the red blood cells, with very little in plasma, and the converse was observed for both pentavalent compounds. The authors concluded that trivalent antimony readily enters red blood cells, but that pentavalent antimony does not.

C. METABOLISM

There are recurrent suggestions in the literature that pentavalent antimony is reduced to the trivalent form in the mammalian body. For example, Otto

Table III-3. Average Antimony Levels in Red Blood Cells and Plasma (ug/g) at Various Intervals After im Injection of Trivalent Antimony (Anthiomaline and M.A.T) or iv Injection of Pentavalent Antimony (Solustibosan and Neostibosan)

Chemical	Dose mg Sb/kg	Cells/ Plasma	Time (hours) 0.25	1	3	6	12	24
Anthiomaline	0.5	Cells	.26	.78	.68	.36	.19	.15
		Plasma	.13	.18	.13	.11	.11	.03
M.A.T.	0.5	Cells	--*	1.1	.79	.44	.35	.35
		Plasma	--	.12	--	.08	.05	.07
Solustibosan	3.0	Cells	3.9	1.1	.3	.4	0	.2
		Plasma	11.8	6.3	2.4	1.1	.3	.3
Neostibosan	2.0	Cells	1.3	.8	.7	.6	.3	.3
		Plasma	10.9	5.0	3.3	2.1	1.1	.8

*-- Not reported.

SOURCE: Adapted from Otto et al. (1947).

and Maren (1950) found large amounts of antimony in erythrocytes following im injection of stibanose (6 mg Sb(V)/kg) in dogs. Previous results from this group (Otto et al., 1947) and others (Molokhia and Smith, 1969) had shown that Sb(V) does not enter erythrocytes but that Sb(III) does, suggesting that, in this case, the Sb(V) had been reduced to Sb(III). Otto and Maren (1950) did not detect antimony accumulation in erythrocytes following an im dose of 0.5 mg Sb(V)/kg or entry into red cells following iv injection of either 0.5 or 5 mg Sb(V)/kg. The authors stated that the available data were not sufficient to support a conclusion regarding possible reduction of Sb(V) to Sb(III).

Goodwin and Page (1943) used polarography to analyze the valence state of antimony in the blood and urine of humans injected iv with Sb(V). During the first 12 hours after the administration of pentavalent antimony (sodium antimony gluconate equivalent to 50 ug/Sb), 83.5% (average of three subjects) of the administered dose was excreted in the urine as pentavalent antimony. Only 2.5% of the administered dose was excreted as trivalent antimony during the same period, indicating that reduction of Sb(V) to Sb(III) was slight. Otto and Maren (1950) pointed out that some of the Sb(III) found in urine may have been formed during sample preparation in hydrochloric acid for polarographic examination.

D. EXCRETION

Otto and Maren (1950) reviewed the routes of excretion of parenterally administered antimony in the mouse, white rat, hamster, guinea pig, rabbit, dog, and human. Trivalent antimony was excreted via the feces and urine. With the exception of the mouse, pentavalent antimony was excreted primarily in the urine (Figure III-2). While the percent of the dose excreted in the feces was less than 5% for all species tested, the percent excreted in the urine was approximately 80, 60, 65, 70, 10, and 43% in the white rat, hamster, guinea pig,

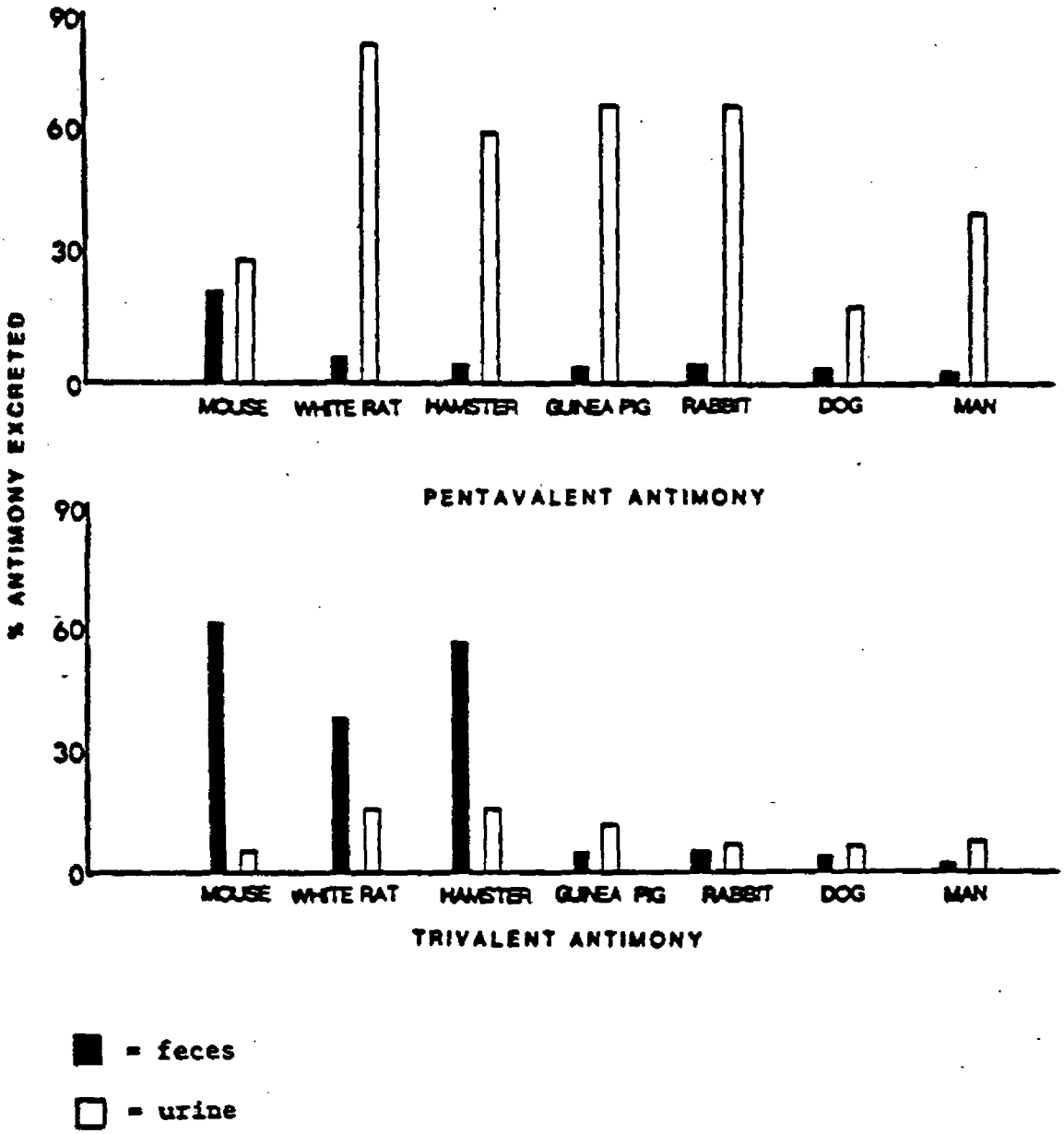


Figure III-2. Excretion of trivalent and pentavalent antimony by several species.

SOURCE: Adapted from Otto and Maren (1950).

rabbit, dog, and human, respectively. Casals (1972) investigated the excretion of antimony in female mice and rats. Female mice were injected im either with antimony dextran glucoside (RL-712) (52 mg Sb/kg) or with N-methyl-glucamine-antimonate (glucantime) (50.3 mg Sb/kg). Female albino rats were injected im with RL-712 (50 mg Sb/kg). The urine was collected for 48 hours. Excretion of antimony in urine was low. In 48 hours, only 12 and 10% of the doses administered were excreted in the urine of mice and rats, respectively.

Van Bruwaene et al. (1982) studied the excretion and tissue distribution of antimony in lactating cows. Three cows (weight 423, 420, and 402 kg) were given a single oral dose of $^{124}SbCl_3$ (2.84, 2.72, and 2.00 mCi, respectively). Since the compound had a specific activity of 3.5×10^{-2} mCi/mmol, the average dose corresponds to 21.1 mg Sb/kg. Total excretion of antimony in feces was triphasic and amounted to about 82% of the dose. Most of the radioactivity in the feces appeared shortly after dosing ($t_{1/2}$ = 0.91 day). About 5% was excreted more slowly ($t_{1/2}$ = 3.3 days), and a small amount, 0.002% of the dose, was excreted with a half-life of 29.1 days. Excretion into urine was biphasic and amounted to a total of 1.1% of the dose. Most of the urinary radioactivity appeared in the initial phase ($t_{1/2}$ = 0.97 day), and about 0.003% of the dose appeared in the second phase ($t_{1/2}$ = 4.6 days). Excretion of antimony in milk was also biphasic and amounted to a total of 0.008% of the dose. Radioactivity in tissues, at 102 days after dosing, amounted to a total of 0.024% of the oral dose. Highest values of radioactivity were found in the spleen, liver, bone, and skin. In a parallel study, one cow (533 kg) received an iv injection of $^{124}SbCl_3$ (0.234 mCi), which corresponds to a dose of 1.5 mg Sb/kg. Excretion of antimony in feces was triphasic and amounted to a total of 2.4% of the injected dose. Excretion of antimony accounted for 51% of the dose in urine

and for 0.08% in milk. At 70 days after dosing, almost 16% of the dose was still in the body. Of the retained dose, 60.8% was found at the site of injection (heart) and 25.2% in the liver. The combined data suggest that very little of the administered dose is absorbed via the gastrointestinal tract of ruminants (see Section III.A, Absorption).

Lippincott et al. (1947) administered potassium antimony tartrate (0.566 to 0.576 g of antimony over 25 days) or fuadin (0.566 to 0.576 g of antimony over 29 days) parenterally to humans as treatment for infection with Schistosoma japonicum. The average 24-hour urinary antimony excretion in the potassium antimony tartrate group ranged from approximately 12% of the administered dose at the beginning of treatment to 25% at the end of treatment. In the fuadin group, the 24-hour excretions ranged from 17% at the beginning of treatment to 42% toward the end of treatment. Toward the end of the treatment, the combined excretion of antimony in urine and feces in 48 hours was roughly 55% of the administered dose. Monkeys administered iv doses of piperazine diantimonyl tartrate or potassium antimony tartrate had maximum excretion of antimony 24 hours postdosing (Abdel-Wahab et al., 1974).

Otto et al. (1947) studied excretion of antimony in humans (see Section III.B, Distribution). Fourteen black adult males with filiaria were treated for 5 days by daily im injection: six were administered lithium antimony thiomalate (up to 21 daily doses of 0.5 mg Sb(III)/kg); three were administered monosodium antimony thioglycollate (up to 11 daily doses of 0.5 mg Sb(III)/kg); two were administered iv injections twice daily of neostibosan (2 to 4 mg Sb(V)/kg/dose); and three were administered iv injections twice daily of stibanose (3 to 6 mg Sb(V)/kg/dose). The amount of antimony excreted in 24 hours in urine and feces was measured colorimetrically after the first dose and

at the end of the treatment. In all cases, most of the excreted antimony appeared in urine, with only low levels appearing in feces (Table III-4). The pentavalent forms of antimony were excreted in urine more rapidly than the trivalent forms. The authors speculated that these differences reflected the differences in plasma concentration (Sb(V)>Sb(III)) known to occur (see Section III.B, Distribution).

E. BIOACCUMULATION AND RETENTION

Gerber et al. (1982) measured whole-body (except intestinal tract) levels of ^{125}Sb in pregnant mice (BALB/c strain) fed tracer levels of $^{125}SbCl_3$ in the diet. The diet was started from the day of the vaginal plug. The values obtained (expressed as percent of daily dose) on days 2, 4, and 6 were 0.26 $\pm$ 0.07%, 1.92 $\pm$ 0.51%, and 1.53 $\pm$ 0.93%, respectively. The authors concluded that a steady-state level of 1.7% was reached by day 4. The authors also studied the kinetics of ^{125}Sb loss from pregnant mice injected ip with $^{125}SbCl_3$ on day 12 of pregnancy. The label was lost in a biphasic fashion (Figure III-3), with the two components having half-times of about 6 hours (representing about 95% of the dose) and 2.4 $\pm$ 0.3 days (representing about 5% of the dose). A similar biphasic clearance of label from a number of tissues was observed following ip injection of $^{125}SbCl_3$, but half-lives were not estimated. In another test, mice were fed $^{125}SbCl_3$ (tracer levels) during pregnancy and for 15 days after delivery. When exposure ceased, antimony was cleared biphasically, with half-lives of 1.84 $\pm$ 0.22 days and 96 $\pm$ 48 days (the latter representing 3.1% $\pm$ 0.7% of the total). The half-life of antimony in the newborns was estimated to be about 10 days.

Bradley and Fredrick (1941) studied antimony levels in albino rats and rabbits following chronic exposure. Several series of tests were performed in

Table III-4. Excretion of Antimony in Humans Following Repeated Administration of Antimony[a]

Chemical	Valence	After first treatment[a]		End of treatment	
		Urine	Feces	Urine	Feces
Lithium antimony thiomalate	+3	11.4	0.2	21.6[b]	2.2[b]
Monosodium antimony thioglycollate	+3	8.1	1.3	70[b]	--
Stibanose	+5	43.0	0.02[b]	67	0.8
Neostibosan	+5	16.7	0.12[b]	55	8.4

[a]Excretion is expressed as percentage of daily dose excreted in 24 hours.
[b]Single value.

SOURCE: Adapted from Otto et al. (1947).

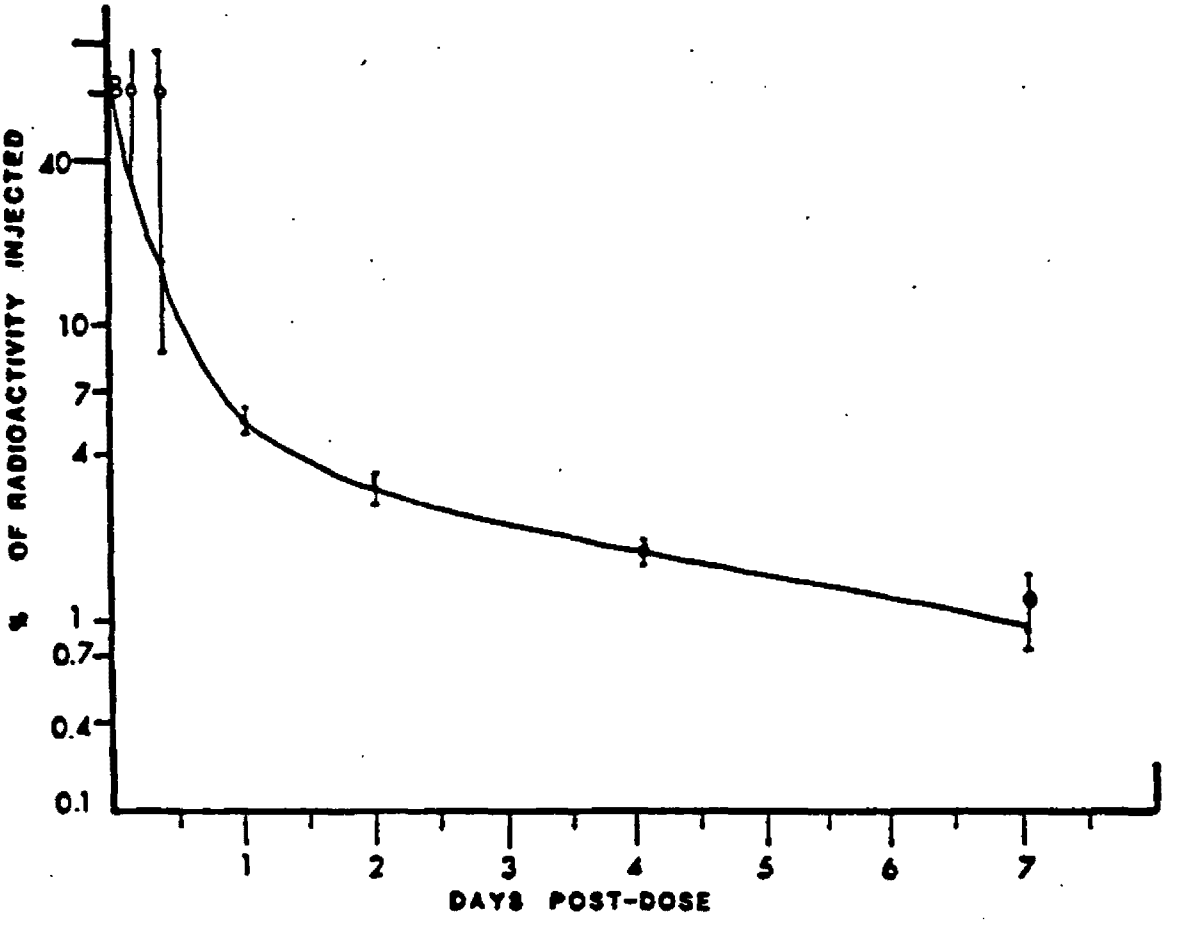


Figure III-3. Whole-body radioactivity of mice following a single intraperitoneal injection of $^{125}SbCl_3$.

SOURCE: Adapted from Gerber et al. (1982).

which rats were fed potassium antimony tartrate (8 mg Sb/kg/day) or antimony metal (8 or 40 mg Sb/kg/day) in the diet for 6 or 12 months. In another test, rats were fed potassium antimony tartrate (8 mg Sb/kg/day) or antimony metal (40 mg Sb/kg/day) for 7-1/2 months ad libitum. In a third test, potassium antimony tartrate was fed to rats for 6 months in doses increasing to 100 mg Sb/kg/day and then maintained at that level for an additional 6 months. Antimony metal was fed similarly to another group of rats by increasing the dose to 1 g Sb/kg/day. Rabbits were fed potassium antimony tartrate or antimony metal at a dose of 8 mg Sb/kg/day or 40 mg Sb/kg/day, respectively, for 4 months. Antimony content of body tissues was measured semiquantitatively by chemical and spectrographic methods. An average of 1 mg of Sb was found in the carcasses of antimony-exposed rats, regardless of the daily dose, while control animals contained an average of 0.1 mg Sb. The authors concluded that antimony does not accumulate to any extent in the animals.

Bomhard et al. (1982) studied accumulation of antimony in rats (SPF-derived Wistar TNO W74) following subchronic oral exposure to two antimony-containing pigments. The pigments were nickel rutile yellow [$(Ti_{0.88}Sb_{0.05}Ni_{0.075})O_2$] and chrome rutile yellow [$(Ti_{0.94}Sb_{0.03}Cr_{0.03})O_2$]. On a weight basis, these pigments contain 7.2 and 4.4% antimony, respectively. Groups of 15 male and 15 female Wistar TNO W74 rats (4 to 5 weeks old) were fed diets containing 0, 10, 100, 1,000 or 10,000 ppm of these pigments for 3 months. Assuming a mean body weight of 0.3 kg and food consumption of 15 g/day (Arrington, 1972), this corresponds to average daily doses of about 0, 0.036, 0.36, 3.6, or 36 mg Sb/kg/day from nickel rutile yellow and of 0, 0.022, 0.22, 2.2, or 22 mg Sb/kg/day from chrome rutile yellow. No measurable accumulation (<5 ppb) of antimony in liver or kidney was observed in animals receiving doses up to 1,000 ppm of either pigment for 3 months.

Schroeder et al. (1968) studied antimony accumulation in mice following chronic exposure. Groups of about 54 male and 54 female Charles River CD strain mice were supplied with water containing 0 or 5 ppm Sb (as potassium antimony tartrate) from the time of weaning until death. This corresponds to an average daily dose of about 0.83 mg Sb/kg/day, assuming mean body weights of 0.03 kg and water consumption of 5 mL/day (Arrington, 1972). When death occurred, samples of heart, lung, kidney, and spleen were removed and pooled in groups of 5 to 15 as a function of age. Samples were ashed at low temperature and analyzed by atomic absorption spectrophotometry. The results are shown in Table III-5. Antimony was measurable in 17 to 60% of the tissue samples at concentrations of 6 to 14 ug Sb/g wet weight.

Schroeder et al. (1970) also studied antimony accumulation in rats following chronic exposure. Groups of 100 or more Long-Evans rats (at least 50 of each sex) were supplied with drinking water containing 0 or 5 mg Sb/L (as potassium antimony tartrate) from the time of weaning until death. This corresponds to an average daily dose of about 0.43 mg Sb/kg/day, assuming mean body weight of 0.35 kg and water consumption of 30 mL/day (Arrington, 1972). When death occurred, samples of tissues were removed, pooled in lots of two to eight, ashed at low temperature, extracted in 2% ammonium pyrrolidine dithiocarbamate, and analyzed for antimony content by atomic absorption spectrophotometry. The extraction procedure improved the sensitivity of the analysis over the previous study. Mean antimony levels in tissues from treated animals of all ages were found to range from about 10 to 18 ug Sb/g dry weight. Antimony levels were found to increase with age over the interval of 9 to 35 months of age (correlation coefficient = 0.525, $p < 0.05$).

Table III-5. Mean Antimony Levels in Tissues of Mice Following Lifetime Exposure to Potassium Antimony Tartrate in Water

	Control mice		Antimony-exposed mice[a]		
Tissue	No.	ug/g[b]	No.	% found[c]	ug/g[b]
Kidney	19	ND[d]	60	25	13
Liver	38	ND	48	51	6
Heart	19	ND	88	17	9
Lung	19	ND	61	60	11
Spleen	19	ND	78	19	14

[a]Animals were supplied with water containing 5 ppm Sb
[b]from weaning until death.
[c]ug Sb/g wet weight of tissue; these values are approximately ± 25%.
[d]% found is percent of samples with measurable Sb levels.
not detected.

SOURCE: Adapted from Schroeder et al. (1968).

Swanson and Truesdale (1971) measured antimony concentration in normal and cataractous human lens tissue. Low or undetectable levels were found in the younger age groups (0 to 5 and 10 to 20 years). Some accumulation was noted in older age groups (50 to 60 and 70 to 85 years). Antimony concentration levels in cataractous tissue (age groups 40 to 55, 60 to 75, and 80 years and over) were somewhat higher than in age-matched normal tissue. The authors suggest that antimony accumulation in the lens might be age-dependent.

The levels of antimony in human milk and tissues have also been determined in several studies. Clemente et al. (1982) studied the concentrations of antimony and other elements in human milk obtained from subjects in Italy. More than 130 samples were obtained from 21 women for about 2 to 3 months starting 15 days after childbirth. A mean $\pm$ SD of 3.0 $\pm$ 0.4 ng Sb/g of milk (wet basis) was reported for 49 samples of milk obtained from 16 women with antimony levels above the detection limit of 0.05 ng Sb/g. Antimony values ranged from less than 0.05 to 12.9 ng/g among the 21 subjects.

Demmel et al. (1982) reported a mean antimony concentration of 17.51 x 10-8 g/g dry weight in 90 pineal glands obtained from humans of both sexes.

Lindh et al. (1980) studied antimony levels in bone tissue of industrially exposed workers. Specimens of femur were collected during autopsy of seven workers employed more than 10 years at a smelting and refining plant in Sweden. The ages ranged from 45 to 75 years, and the time between retirement and death ranged from 0 to 21 years. Antimony levels in bone ranged from less than 0.02 to 0.58 ppm, with a median of 0.015 ppm. Control values, obtained from five individuals, ranged from 0.007 ppm to 0.1 ppm, with a median of 0.007 ppm.

F. SUMMARY

About 7 to 15% of an oral dose of trivalent antimony is absorbed in rodents and about 2% in ruminants (cows). Very little trivalent or pentavalent antimony was absorbed when introduced into the gastrointestinal tract of Syrian hamsters. No estimate of gastrointestinal absorption was found in humans. Absorbed antimony usually distributes to most tissues of the body, with some preferential accumulation in bone, thyroid, and adrenal. In mice injected im with either antimony dextran glucoside or N-methyl-glucamine antimonate, the compounds were absorbed from the site of injection and deposited in the liver and spleen. Trivalent antimony is readily taken up by red blood cells, but pentavalent antimony does not enter the red blood cells.

Claims have been made that Sb(V) is reduced to Sb(III) in the body, but no strong evidence exists to support this hypothesis. Pentavalent antimony is excreted primarily in the urine in most species (including humans). In the mouse, white rat, hamster, guinea pig, rabbit, dog, and human, trivalent antimony is excreted both in urine and in feces, the ratio depending upon the species. In cows, 82% of the total dose was excreted in the feces, 1.1% in the urine, and 0.008% in the milk when $^{124}SbCl_3$ was administered orally. When $^{124}SbCl_3$ was given intravenously to cows, 2.4% of the total dose was excreted in feces, 51% in the urine, and 0.08% in the milk.

There appears to be minimal accumulation of antimony in the body, although antimony has been reported in human milk and tissues. A mean $\pm$ SD of 3.0 $\pm$ 0.4 ng Sb/g of milk (range <0.05 to 12.9 ng/g) was reported in Italian women. A mean concentration of 17.51 x 10-8 g/g dry weight of 90 pineal glands was reported in humans of both sexes. A median concentration of 0.015 ppm was found in the bone tissue of industrially exposed workers, compared to 0.007 ppm in the

nonindustrial control group. In mice fed $^{125}SbCl_3$ in the diet, a steady-state whole-body level was reached after 4 days. Following ip injection in mice, antimony was cleared from the body biphasically, with a rapid phase ($t_{1/2}$ = 6 hours) accounting for about 95% of the dose, and a slow phase ($t_{1/2}$ = 2.4 days) accounting for 5% of the dose. In mice fed antimony in the diet during pregnancy and 15 days postpartum, antimony was cleared biphasically, with half-times of 1.8 and 96 days when exposure was discontinued. In mice exposed to 0.8 mg Sb/kg/day for life, tissue levels of antimony were only 6 to 14 ug Sb/g tissue. Similar results were obtained in rats exposed to 0.4 mg Sb/kg/day for life, although levels tended to increase somewhat with age ($p < 0.05$).

IV. HUMAN EXPOSURE

This chapter will be supplied by the Science and Technology Branch, Criteria and Standards Division, Office of Drinking Water.

V. HEALTH EFFECTS IN ANIMALS

A. SHORT-TERM EXPOSURE

1. Lethality

A summary of acute lethality data for antimony and several antimony compounds is shown in Table V-1. Estimates of oral LD_{50} values range from 15 mg Sb/kg in the rabbit to 600 mg Sb/kg in the mouse. The LD_{50} value of a single intraperitoneal (ip) implantation of elemental antimony is 100 mg/kg in the albino rat and 150 mg/kg in the guinea pig (Bradley and Fredrick, 1941). Large multiple doses (>55 mg) of the element are lethal when fed to rabbits (Carozzi, 1930). Rats survived oral doses of 700 mg elemental antimony but failed to gain weight (Bradley and Fredrick, 1941). Potassium antimony tartrate is roughly 10 times more toxic than the elemental form, while other salts of antimony are less toxic.

Girgis et al. (1965) found that mice developed tolerance to ip doses of potassium antimony tartrate. The ip LD_{50} of potassium antimony tartrate was 49 ± 1 mg/kg in untreated male white mice. This corresponds to a dose of 18 mg Sb/kg. After an initial nonlethal ip dose of 35 mg/kg potassium antimony tartrate, there was an increase of about 50% in the LD_{50} (to approximately 75 mg/kg potassium antimony tartrate).

Ghaleb et al. (1979) investigated the acute toxicity of five organic trivalent antimonials in mice and compared it to that of tartar emetic (potassium antimonyl tartrate, 36.47% Sb). Estimates of the ip LD_{50} values of these compounds ranged from 13 to 329 mg Sb/kg and are listed on page V-3.

Table V-1. Acute Toxicity of Antimony

Compound	Species	Route[a]	Dose (mg Sb/kg)	Reference
Sodium antimony tartrate	Mouse	ip	LD_{50} = 24	Ercoli (1968)
	Mouse	sc	LD_{50} = 19	Ercoli (1968)
Potassium antimony tartrate (tartar emetic)	Mouse	po	LD_{50} = 600	HSDB (1987)
	Mouse	ip	LD_{50} = 50	HSDB (1987)
	Mouse	sc	LD_{50} = 20	Ercoli (1968)
	Mouse	ip	LD_{50} = 49	Girgis et al. (1965)
	Mouse	ip	LD_{50} = 18	Ghaleb et al. (1979)
	Mouse	iv	LD_{50} = 24	Ercoli (1968)
	Mouse	iv	LD_{50} = 45	HSDB (1987)
	Mouse	sc	LD_{50} = 55	HSDB (1987)
	Rat	po	LD_{50} = 300	Bradley and Fredrick (1941)
	Rat	po	LD_{50} = 115	HSDB (1987)
	Rat	ip	LD_{50} = 11	Bradley and Fredrick (1941)
	Rat	im	LD_{50} = 33	HSDB (1987)
	Guinea pig	ip	LD_{50} = 15	Bradley and Fredrick (1941)
	Guinea pig	im	LD_{Lo} = 55	HSDB (1987)
	Rabbit	po	LD_{50} = 15	HSDB (1987)
	Rabbit	iv	LD_{50} = 15	HSDB (1987)
Antimony	Mouse	ip	LD_{50} = 90	HSDB (1987)
	Rat	ip	LD_{50} = 100	Bradley and Fredrick (1941)
	Guinea pig	ip	LD_{50} = 150	Bradley and Fredrick (1941)
Antimony trifluoride	Mouse	sc	LD_{50} = 22.9	Levina and Chekunova (1965)
Sb (OH) (COONa) (Na Acr.) Naphth.[b]	Mouse	ip	LD_{50} = 329	Ghaleb et al. (1979)
Sb (OH)2(UH) Me Pyr.[b]	Mouse	ip	LD_{50} = 305	Ghaleb et al. (1979)
Sb (OH) (COONa) Naphth.[b]	Mouse	ip	LD_{50} = 61	Ghaleb et al. (1979)
Sb (OH)2 Pyr.[b]	Mouse	ip	LD_{50} = 147	Ghaleb et al. (1979)
Sb Form (OH) QS.[b]	Mouse	ip	LD_{50} = 13	Ghaleb et al. (1979)

[a] Abbreviations used: ip = intraperitoneal, iv = intravenous, sc = subcutaneous, po = peroral, im = intramuscular.

[b] Defined in text on following page.

- Antimonyl 2-hydroxy,3-carboxy,1-sodium acrylate naphthalein "Sb (OH) (COONa) (Na Acr.) Naphth." 17.40% Sb; LD_{50} = 1,750 mg/kg (329 mg Sb/kg).
- Antimonyl-2,4-dihydroxy-5-hydroxymethyl pyrimidine "Sb (OH)2(OH) Me Pyr." 46.27% Sb; LD_{50} = 660 mg/kg (305 mg Sb/kg).
- Antimonyl-2-hydroxy-1,3-dicarboxy sodium naphthalein "Sb (OH) (COONa) Naphth." 18.80% Sb; LD_{50} = 350 mg/kg (61 mg Sb/kg).
- Antimonyl-2,4-dihydroxy pyrimidine "Sb (OH)2 Pyr." 48.993% Sb; LD_{50} = 300 mg/kg (147 mg Sb/kg).
- Antimonyl-7-formyl-8-hydroxyquinoline-5-sulfonate "Sb Form (OH) QS." 17.72% Sb; LD_{50} = 75 mg/kg (13 mg Sb/kg).

The emetic dose of six antimony compounds in 6.5- to 7.5-kg dogs was determined by Flury (1927). In each case, antimony trioxide (one dog), antimony pentoxide (one dog), sodium antimonate (one dog), potassium antimonate (three dogs), and sodium meta-antimonate (two dogs) were suspended with gum arabic in water; potassium antimony tartrate (three dogs) was dissolved in 50 g of water and was administered via stomach tube. Table V-2 presents the results of the experiments. Potassium antimony tartrate was the most effective compound causing emesis at 33 mg/kg (about 12 mg Sb/kg). A dose of 16 mg/kg (about 6 mg Sb/kg) produced no apparent effect. Flury added that when very concentrated solutions were administered (concentrations not given) to fasting dogs, the emetic dose was as low as 4 mg/kg (about 1.5 mg Sb/kg).

Cats appear to be more sensitive than dogs to the emetic effect of potassium antimony tartrate. Flury (1927) observed emesis in three cats given 11.5 or 14.3 mg/kg (4.3 or 5.4 mg Sb/kg) in 50 mL of water via stomach tube. In one cat that received a dose of 7.2 mg/kg potassium antimony tartrate (2.7 mg Sb/kg), vomiting did not occur but marked salivation (a common precursor of emesis) was observed. One cat dosed with 6.9 mg/kg (2.6 mg Sb/kg) showed no apparent response.

Table V-2. Emetic Dose of Antimony Compounds in Dogs

Compound	Dose (mg/kg)	Remarks
Antimony trioxide	430	No effects
Antimony pentoxide	400	No effects
Sodium antimonate	460	Nausea
Potassium antimonate	440	Nausea
Potassium antimonate	440	Emesis
Sodium meta-antimonate	400	No effects
Sodium meta-antimonate	530	Nausea
Potassium antimony tartrate	49	Emesis
Potassium antimony tartrate	33	Emesis
Potassium antimony tartrate	16	No effects

SOURCE: Adapted from Flury (1927).

Bradley and Fredrick (1941) observed the toxic response in albino rats following a single ip injection of antimony (metal) or five of its compounds (potassium antimony tartrate, antimony trisulfide, antimony pentasulfide, antimony trioxide, antimony pentoxide) at dose levels up to the minimum lethal dose (100, 11, 1,000, 1,500, 3,250, 4,000 mg Sb/kg, respectively). Animals dying within a few days showed dyspnea, loss of weight, general weakness, loss of hair, and myocardial insufficiency. In surviving animals, prominent signs included immediate weight loss (slowly regained after 5 to 10 days), marked loss of hair; dry, scaly skin; and eosinophilia. At necropsy, gross examination revealed myocardial congestion with engorgement of coronary vessels and dilation of the right heart. Death was attributed to myocardial failure. Other signs included congestion and occasional necrosis in spleen, liver, and kidney, and hemorrhages in the small intestine.

Bromberger-Barnea and Stephens (1956) studied the in vivo and in vitro acute effects of antimony on canine hearts. Isolated canine hearts were injected with 30 mg potassium (or sodium) antimony tartrate/kg tissue weight (11.2 mg Sb/kg). There was bradycardia and a progressive fall in myocardial contractile force, which was nonreversible. The authors suggested that some antimony became bound to the heart tissue and continued to exert its toxic effects. Single-cell transmembrane potential was unchanged. In intact animals, a single iv injection of 30 mg potassium antimony tartrate/kg (11.2 mg Sb/kg) was lethal within 2 hours postdosing. There was a progressive decrease in contractile force and a fall in systemic blood pressure as well as changes in the S-T segment of the electrocardiogram. Death was preceded by myocardial insufficiency and ventricular fibrillation.

Girgis et al. (1970) studied the effect of antimony injection on electrocardiograms (standard limb leads I, II, and III and augmented leads AVR, AVL, and AVF) in mongrel dogs. The dogs were given 5 mg sodium antimony tartrate/kg (2.0 mg Sb/kg) by iv injection for 4 successive days. Electrocardiographic changes occurred immediately after treatment. There was a decrease in the P-wave amplitude, a decrease in the QRS complex amplitude with no prolongation of QRS interval, a flattened or depressed S-T segment, and a decrease in amplitude and inversion of the T-wave.

2. Other Effects

Flury (1927) fed high doses of five antimony compounds to rats (one per chemical) for 9 days. Each rat received daily doses increasing from 100 mg to 2 or 3 g. Doses up to 2 g/day of antimony trioxide or antimony pentoxide or up to 3 g/day of sodium meta-antimonate caused no adverse effects. Potassium antimony tartrate was found to be toxic, however, causing death after the daily dose was increased to 500 mg (about 1,100 mg/kg Sb/kg) on day 7. Potassium antimonate produced adverse effects at dose levels of 2 g/day, but recovery was rapid when dosing ceased.

Pribyl (1927) investigated the effect of repeated exposure to 15 mg potassium antimony tartrate/kg/day (given in a milk plus sugar solution) over a 7- to 22-day period on nitrogen metabolism and toxicity in four rabbits. This corresponds to a dose of 5.6 mg Sb/kg/day. Nonprotein nitrogen, urea nitrogen, and ammonia nitrogen were measured in the blood and urine of each animal before and after exposure. A small rise (10 to 13%) in nonprotein nitrogen in blood and urine was observed (no p value given); this was partly due to an increase in urea nitrogen. Mean urine ammonia nitrogen was also slightly increased (7%,

no p value given). The author interpreted these increased nitrogen levels in blood and urine as evidence of increased protein catabolism in tissues. Gross and microscopic examination showed hemorrhagic lesions in the stomach and small intestine, liver atrophy with fat accumulation and congestion, and hemorrhage in the kidney cortex, with some tubular necrosis.

Hashash et al. (1981) induced inner ear pathology in adult guinea pigs with two antimonial antibilharzial drugs (eight animals/drug). In each group, half of the animals were injected intramuscularly (im) for 15 days with the therapeutic dose, and half were injected im for 15 days with the experimental dose (twice the therapeutic dose). The therapeutic doses were 1 mg/kg of Stibophen NF (sodium antimony bis(pyrocatechol-2,4-disulfate)) and 0.7 mg/kg of Bilharcid EP (piperazine-di-antimonyl tartrate). The test doses were 2 mg/kg and 1.4 mg/kg for Stibophen NF and Bilharcid EP, respectively. Tissue changes occurred after the 15-day treatments. Atrophy of the organ of Corti and replacement by granular, vacuolated epithelioid cells were seen in the animals receiving experimental doses of either drug. The spiral ganglion was not affected. The therapeutic dose caused patchy hydropic degeneration of the hair and supporting cells of the organ of Corti. The therapeutic dose of piperazine-di-antimonyl tartrate caused generalized degeneration of the same tissues.

B. LONG-TERM EXPOSURE

1. Subacute/Subchronic Toxicity

Westrick (1953) studied the effects of feeding antimony for 7 weeks on thyroid function in rats. Four groups of five male Sprague-Dawley rats (initial mean body weight about 120 g) were fed diets containing 0 or 2% Sb_2O_3 for 7 weeks. In addition, one group each of the 0 and the 2% Sb_2O_3 diet received

thyroxin injections. Using a mean body weight of 0.18 kg (the mean of reported initial and final weights) and assuming average food consumption of 12 g/day (Arrington, 1972), this corresponds to an average daily dose of 1,114 mg Sb/kg/day. Animals were weighed periodically, and oxygen consumption (an index of thyroid activity) was measured after 1, 2, 3, 4, and 6 weeks. Growth was not affected in the antimony-treated rats, but there was a drastic weight loss at 4 weeks in the antimony-thyroxin-treated rats.

After 2 weeks, there was a significant ($p < 0.01$) increase in oxygen consumption in the antimony-thyroxin-treated group. The author suggested that antimony enhances the action of thyroxin, causing hypermetabolism. Since these changes were not accompanied by changes in the thyroid histopathology, the action of antimony plus thyroxin was judged to be extrathyroidal. The antimony-treated group had some thyroid hyperplasia, suggesting a thyroid block. Similar results (hypermetabolism) were observed in two adult male rabbits dosed by capsule with 13 mg Sb_2O_3/kg/day (10.9 mg Sb/kg/day) for 20 days.

Flury (1927) performed an extensive series of studies on the health effects of orally ingested antimony in animals. In the first study, rats (two per test group) were exposed to potassium antimony tartrate or potassium antimonate (dissolved in water), or to antimony trioxide or antimony pentoxide (mixed with dextrose) in food. Doses began at 0.1 mg/day and were increased periodically over the course of 107 days to a final level of 4 mg/day. For most of the period, both animals received a low dose (0.1 mg/day for the first 21 days and 0.2 mg/day for the next 50 days); one of each pair of rats then received daily doses that were doubled each week to reach the final level for the last 5 days. No toxic effects were observed, and growth was unaffected except for a stimulation of growth at low doses.

In the second study, Flury (1927) tested higher doses of potassium antimony tartrate and antimony trioxide and sodium meta-antimonate in food for a slightly longer period, 131 days. Groups of two rats were exposed to doses of the first two compounds beginning at 1 mg/day for 45 days, and then increasing over the course of 86 days to 200 mg/day, with the dose being doubled in an irregular fashion. The third compound was given in doses from 3 to 1,000 mg/day in a similar pattern. No effects were seen, even at the highest doses, for antimony trioxide and sodium meta-antimonate, but potassium antimony tartrate caused a generalized deterioration and death at high doses (200 mg/day). This corresponds to about 485 mg Sb/kg/day, assuming a mean body weight of 155 g (approximately 130 to 180 g).

Bomhard et al. (1982) studied the subchronic oral toxicity of two antimony-containing pigments fed to rats for 91 days. The pigments were nickel rutile yellow $[(Ti_{0.88}Sb_{0.05}Ni_{0.075})O_2]$ and chrome rutile yellow $[(Ti_{0.94}Sb_{0.03}Cr_{0.03})O_2]$. On a weight basis, these pigments contain 7.2 and 4.4% antimony, respectively. Groups of 15 male and 15 female Wistar TNO W74 rats (4 to 5 weeks old) were fed diets containing 0, 10, 100, 1,000, or 10,000 ppm of these pigments for 91 days. Assuming a mean body weight of 0.3 kg and food consumption of 15 g/day (Arrington, 1972), this corresponds to daily doses of about 0, 0.036, 0.36, 3.6, or 36 mg/kg/day from nickel rutile yellow or 0, 0.022, 0.22, 2.2, or 22 mg Sb/kg/day from chrome rutile yellow. Appearance, behavior, food consumption, growth, mortality, hematological and clinical chemical data, organ weights, and gross and microscopic appearance of organs were not affected in any dose group.

Potkonjak and Vishnjich (1983) injected female "Wistar-type" albino rats with 0.5 mL of Sb_2O_3 or Sb_2O_5 suspension (50 mg of dust) ip in one group and

endotracheally in another group. The animals were sacrificed after 2 months, and the lungs and omentum were examined histologically. Pneumoconiosis of a noncollagenous nature was observed.

Kazem et al. (1980) demonstrated that male albino rats repeatedly injected with ^{99m}TC-antimony-sulfide colloid (693 ug Sb, given in nine equivalent doses at 1-week intervals) showed no macroscopic or microscopic evidence of tissue or cellular damage in the liver, spleen, kidneys, or bone marrow. The total dose administered corresponds to 2 mg Sb/kg, assuming a mean body weight of 0.35 kg (Arrington, 1972).

2. Chronic Toxicity

Bradley and Fredrick (1941) studied the chronic toxicity of antimony in albino rats and rabbits. Several series of tests were performed in which rats were fed potassium antimony tartrate (8 mg Sb/kg/day) or antimony metal (8 or 40 mg Sb/kg/day) in the diet for 6 or 12 months. In another test, rats were fed potassium antimony tartrate (8 mg Sb/kg/day) or antimony metal (40 mg Sb/kg/day) for 7-1/2 months ad libitum. In a third test, potassium antimony tartrate was fed to rats for 6 months in doses that were increased up to 100 mg Sb/kg/day and then maintained at that level for an additional 6 months. Antimony metal was fed similarly to another group of rats by increasing the dose to 1 g Sb/kg/day. Rabbits were fed potassium antimony tartrate or antimony metal at a dose of 8 or 40 mg Sb/kg/day, respectively, for 4 months. All animals maintained their normal growth rates. Basophilic blood cell counts were normal throughout the study period in both rats and rabbits, although rats showed slight leukocytosis. Gross and microscopic examination of tissues from these animals revealed changes similar to those observed in animals receiving sublethal doses of potassium ammonium tartrate by ip injection. These changes

included congestion and altered fiber appearance in the heart, congestion with degeneration and polymorphonuclear leukocyte infiltration in the liver, congestion with glomerulonephritis and tubular necrosis in the kidney, softened and congested viscera with hemorrhages in the small intestine, and congestion of the spleen.

Schroeder et al. (1968) studied the effect of chronic exposure to antimony in mice. Groups of about 54 male and 54 female Charles River CD strain mice were supplied with drinking water containing 0 or 5 ppm Sb (as potassium antimony tartrate) from the time of weaning until death. This corresponds to an average daily dose of about 0.83 mg Sb/kg/day, assuming a mean body weight of 0.03 kg and water consumption of 5 mL/day (Arrington, 1972). Animals were weighed weekly for 8 weeks and then monthly. Antimony did not significantly suppress growth in either males or females during the first year, but did result in weight loss in males after 18 months ($p < 0.025$) and decreased weight gain in females measured at 12 and 18 months ($p < 0.005$). Antimony did not significantly affect the mean or medial lifespan or lifetime until 75, 90, or 100% deaths occurred in either males or females. Upon necropsy, histologic examination of the liver revealed no significant difference in the incidence or degree of fatty degeneration between controls (22.2%) and antimony-exposed animals (16.4%).

The effect of chronic exposure to antimony in rats was also studied (Schroeder et al., 1970). Groups of 100 or more Long-Evans rats (at least 50 males and 50 females) were supplied with drinking water containing 0 or 5 mg Sb/L (as potassium antimony tartrate) from the time of weaning until death. This corresponds to an average daily dose of about 0.43 mg Sb/kg/day, assuming a mean body weight of 0.35 kg and water consumption of 30 mL/day (Arrington,

1972). Antimony was toxic to rats. Mean longevity (in days) ± SE was 1,160 ± 27.8 for control males, 1,304 ± 36.0 for control females, 999 ± 7.8 for treated males, and 1,092 ± 30.0 for treated females. Antimony had a negligible effect on body weight. Serum cholesterol levels were increased in male rats (97.6 ± 4.9 mg/100 mL in treated animals versus 77.5 ± 2.1 mg/100 mL in controls) and decreased in female rats (97.0 ± 5.6 mg/100 mL in treated animals versus 116.0 ± 6.0 in controls). Fasting blood glucose levels were not significantly different in either males or females, but nonfasting blood glucose levels were lower in both males (94.5 ± 6.2 mg/100 mL in treated animals versus 134.4 ± 5.1 mg/100 mL in controls) and females (82.5 ± 7.0 mg/100 mL in treated animals versus 114.2 ± 5.4 mg/100 mL in controls). No significant effects of antimony on glucosuria, proteinuria, heart weight, or heart/body weight ratio were observed. Histopathology was not performed in this study.

C. REPRODUCTIVE/TERATOGENIC EFFECTS

Hodgson et al. (1927) studied the reproductive effects of antimony in rabbits (strain not specified) and English white mice (2 males and 10 females per breeding group). The rabbits (four females/group, 1.8 kg) were injected iv with seven to seventeen 10-mg doses of sodium antimony tartrate (2.2 mg Sb/kg) or nine to sixteen 50-mg doses of an unknown organic antimony compound over 16 to 38 days. The mice were injected hypodermically with 30 to 39 doses of 10 mg of another unknown organic antimony salt over 60 to 77 days. Injections were given to only the males in one breeding group, only the females in two breeding groups, and to both sexes in two breeding groups. In general, in the female rabbits and mice, contraception, abortion, and fetal damage (details not specified) occurred; in males, the antimony salt did not cause sterility.

James et al. (1966) fed antimony potassium tartrate to four yearling ewes at a dose level of 2 mg/kg of body weight for 45 days or throughout gestation. All ewes fed antimony gave birth to normal, full-term lambs. No adverse effects were found in ewes upon necropsy.

Belyaeva (1967) investigated the reproductive effects of inhalation exposure of antimony trioxide in rats. Repeated exposure to 250 mg/m^3 Sb_2O_3 dust over a 2-month period resulted in sterility and fewer offspring in dosed rats than in the control group.

Casals (1972) reported the absence of any abnormalities in rat fetuses whose mothers were exposed to pentavalent antimonial drug RL-712 (antimony dextran glycoside) during gestation. Wistar female rats were administered five im injections of 125 and 250 mg Sb/kg between days 8 and 14 of gestation. On day 20, the dams were sacrificed; the number of fetuses, resorptions, and implantations were recorded, and fetuses were examined for external malformations.

D. MUTAGENICITY

Paton and Allison (1972) studied the effect of antimony on chromosome damage in human leukocytes in vitro. A concentration of 1 uM sodium antimony tartrate was toxic to cells, and incubation for 48 hours with 2.3 nM sodium antimony tartrate caused a significant ($p < 0.05$) increase in cells with chromatid breaks. Cytologic examination revealed that 12% metaphases had chromatid breaks in treated cells, and only 2% had chromatid breaks in control cells.

Hashem and Shawki (1976) studied human peripheral blood lymphocytes (Pls) cultured with or without phytohemagglutinin stimulation from patients treated with potassium antimony tartrate (injected dose = 2 mg/kg, twice each week for 6 weeks). In Pls cultures of treated patients, 4.0 $\pm$ 0.59% of Pls were

transformed into lymphoblasts. Phytohemagglutinin-stimulated cultures had a mitotic index significantly lower than that in cultures from nonantimony-treated patients. There was also an increase in chromosome breaks and fragmentation in the antimony-treated group. Cultures without phytohemagglutinin stimulation did not have a lower mitotic index or increased chromosomal damage between groups.

Kanematsu and Kada (1978) and Kanematsu et al. (1980) determined that antimony trichloride, antimony pentachloride, and antimony trioxide were mutagenic in the rec-assay. An improved rec-assay procedure employing the insertion of a cold intubation before incubation of plates at 37°C was used. Two strains of Bacillus subtilis (H17 and M45) were used. Filter paper disks soaked in metal solution were dropped on streaked agar plates. When the DNA damage is produced by a chemical and subjected to cellular recombination-repair function, the growth of recombination-deficient cells is inhibited much more than that of the wild-type cells. All three compounds (concentrations = 0.005 to 0.5 M) strongly inhibited the cellular growth of a recombination-deficient strain of B. subtilis (M45) as compared with the wild-type strain (H17). The results indicate the DNA-damaging capacities of the three antimony compounds.

El Nahas et al. (1982) studied the cytogenetic effects of potassium antimony tartrate (36.5% antimony) and piperazine antimony tartrate (36.9% antimony) in male rats (Rattus norvegicus). Five rats were dosed within each treated group. Four untreated rats served as control for each dose. Fifty metaphases were studied per rat. The rats were administered ip injections of 2, 8.4, or 14.8 mg potassium antimony tartrate/kg or 1, 10, or 19.1 mg piperazine antimony tartrate/kg. Each dose was given as a single dose or daily for 5 days. Animals were sacrificed at 6, 24, or 28 hours after a single dose or 6 hours after a multiple dose. Chromosomal aberrations in bone marrow cells were observed as

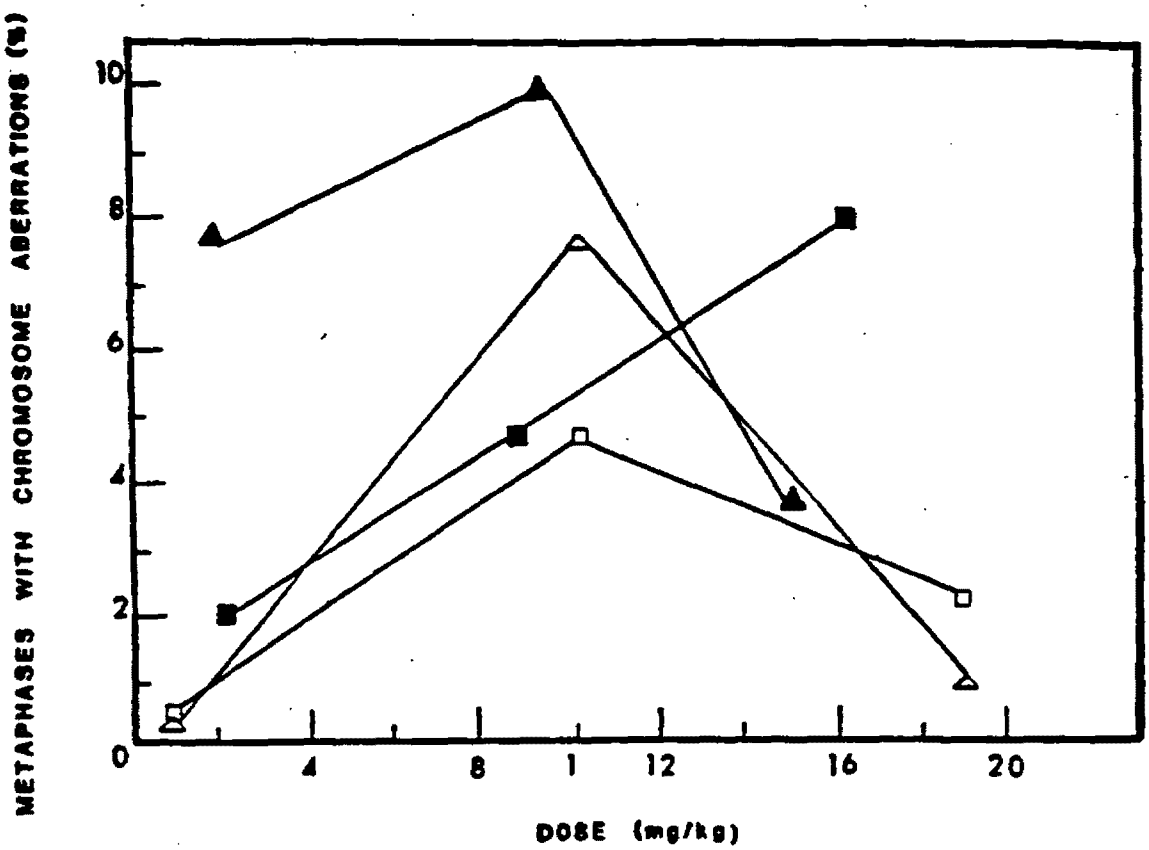
chromatid gaps, chromatid breaks, centric fusions, and chromosomal stickiness. The dose-response of single and multiple treatments of both drugs suggests a maximal effect at the intermediate dose (Figure V-1). The only exception was the single treatment with potassium antimony tartrate, which had a linear response.

The transformation of hamster cells by SA7 virus was enhanced by tungsten antimonate ($WSbO_4$) and $Sb(C_2H_3O_2)_3$ (Casto et al., 1979).

E. CARCINOGENICITY

Schroeder et al. (1968) studied the effect of lifetime exposure to antimony on tumor frequency in mice. The experimental details of this study are reported in Section B.2, Chronic Toxicity. Groups of about 54 male and 54 female Charles River CD strain mice were supplied with drinking water containing 0 or 5 ppm Sb (as potassium antimony tartrate) from the time of weaning until death. This corresponds to an average daily dose of about 0.83 mg Sb/kg/day, assuming a mean body weight of 0.03 kg and water consumption of 5 mL/day (Arrington, 1972). When death occurred, animals were dissected, gross tumors and other lesions were noted, and abnormal tissues were prepared for histologic examination. Tumors were found in 34.8% of control animals and 18.8% of the antimony-treated animals. The authors concluded that antimony exposure had no effect on the incidence or type of spontaneous tumors, either benign or malignant.

Schroeder et al. (1970) studied the effect of lifetime exposure to antimony on tumor frequency in rats. Groups of 100 or more Long-Evans rats (at least 50 of each sex) were supplied with drinking water containing 0 or 5 mg Sb/L (as potassium antimony tartrate) from the time of weaning until death. This corresponds to an average daily dose of about 0.43 mg Sb/kg/day, assuming a mean body weight of 0.35 kg and water consumption of 30 mL/day (Arrington,



□ - Single treatment of piperazine antimony tartrate.

△ - Multiple treatment of piperazine antimony tartrate.

■ - Single treatment of potassium antimony tartrate.

▲ - Multiple treatment of potassium antimony tartrate.

Figure V-1. Dose-response (chromosomal aberrations) of single or multiple doses of potassium antimony tartrate or piperazine antimony tartrate in rats.

SOURCE: Adapted from El Nahas et al. (1982).

1972). No significant effect of antimony exposure on tumor frequency was observed in either male or female animals.

In contrast, recent studies indicate that antimony trioxide is carcinogenic in rats following inhalation exposure. Watt (1983), in a dissertation abstract, reported that antimony trioxide is fibrotic and neoplastic to female rats when inhaled at levels close to the threshold limit values (TLVs). Female CDF rats and S-1 miniature swine were exposed by inhalation to antimony trioxide dust at 1.6 $\pm$ 1.5 mg/m^3 (as Sb) or 4.2 $\pm$ 3.2 mg/m^3 (as Sb) for 6 hours/day, 5 days/week for approximately 1 year. Some rats were held for one year post-exposure (actual data not provided). The doses selected were close to the TLV. The lungs of exposed animals (rats and swine) were mottled and heavier than the lungs of unexposed animals. Serum blood urea nitrogen (BUN) levels were consistently higher though not statistically significant in treated animals. Body weights were significantly higher for exposed rats. Primary lung neoplasms were seen in rats but not in swine. The incidence and/or severity of the response was related to the exposure time and the exposure level. Most of the neoplasms were seen in the higner dose group sacrificed 1 year after exposure and were either scirrhous carcinomas, squamous cell carcinomas, or bronchio-alveolar adenomas. Actual data on incidences of tumors was not provided in the report. The nonneoplastic responses observed in both high- and low-dose groups of rats consisted of focal fibrosis, adenomatous hyperplasia, multinucleated giant cells, cholesterol clefts, pneumonocyte hyperplasia, and pigmented microphages.

Groth et al. (1986) investigated the carcinogenic effects of antimony trioxide and antimony ore concentrate in rats. Three groups of 8-month-old Wistar-derived albino rats (90 males, 90 females per group) were exposed by

inhalation in six Rochester-type stainless-steel exposure chambers (two chambers for each group) to either Sb_2O_3, Sb ore concentrate, or filtered air (control). The mean daily time-weighted averages (TWAs) in Sb_2O_3 chambers were 45.0 (range 0 to 18.5) and 46.0 (range 0 to 91.1) mg Sb_2O_3/m^3. The mean TWAs in Sb ore concentrate chambers were 36.0 (range 0 to 83.2) and 40.1 (range 0 to 91.1) mg Sb ore/m3. The rats were exposed for 7 hours/day, 5 days/week, for up to 52 weeks. Five rats/sex/group were serially sacrificed after 6, 9, and 12 months of exposure. All remaining animals were sacrificed 20 weeks after termination of exposure. Histopathological examinations revealed the presence of lung neoplasms in 27% of the females in the Sb_2O_3 group and 25% of the females in the Sb ore concentrate group. No tumors were found in the male rats or control females. The incidence of lung tumors in females at various intervals is shown in Table V-3.

F. SUMMARY

Estimates of acute oral LD_{50} values in mice and rats range from 115 to 600 mg Sb/kg, although an oral LD_{50} value of 15 mg Sb/kg has been reported for rabbits. The iv and ip LD_{50} values are generally somewhat lower, ranging from 11 to 329 mg Sb/kg.

Early studies showed that there is considerable variation in sensitivity to antimony among species; mice and rats are less sensitive than dogs and cats. In addition, considerable variation in toxicity exists between different chemical forms of antimony; the soluble compounds, especially potassium antimony tartrate, are more toxic than the less soluble oxides.

The most prominent signs of acute oral antimony toxicity are nausea and vomiting, often with diarrhea. In dogs and cats, the emetic dose of potassium

Table V-3. Incidence of Lung Tumors in Female Rats Examined at Specified Intervals

Interval (in weeks)	Incidence of lung tumors		
	Controls	Sb_2O_3	Sb ore
18-40 (died and serial sacrifice)	0/15	0/14	0/14
40 (serial sacrifice)	0/5	0/5	0/5
41-53 (died)	0/10	0/11	1/9
53 (serial sacrifice)	0/5	2/5	2/5
54-71 (died)	0/15	5/23	3/21
71-73 (serial sacrifice)	0/39	12/31(39%)*	11/33 (33%)*
Total (18-73 wk)	0/89	19/89(21%)*	17/87 (20%)*
41-72 wk	0/69	19/70 (27%)*	17/68 (25%)*

*Significantly greater incidences of lung tumors than the controls, $p \leq 0.001$.

SOURCE: Adapted from Groth et al. (1986).

antimony tartrate (in water) is about 12 and 4.2 mg Sb/kg, respectively. In one study (Flury, 1927), exposure of rats and mice to high oral doses of insoluble antimony compounds (e.g., Sb_2O_3, Sb_2O_5) was without effect; however, in another study (Potkonjak and Vishnjick, 1983), ip or endotracheal administration of Sb_2O_3 and Sb_2O_5 suspension (50 mg of dust) caused pneumoconiosis in rats. In yet another study (Pribyl, 1927), lower doses of potassium antimony tartrate (5.6 mg Sb/kg/day) administered in milk for 1 to 3 weeks caused only minor changes in blood and urine nitrogen levels, but produced histological changes in the intestine, liver, and kidneys in rabbits.

Parenteral administration of antimony (as potassium antimony tartrate) at doses of 1.5 to 15 mg Sb/kg results in various signs of myocardial injury. In addition, injury to the inner ear following repeated im injection of antimony bis(pyrocatechol-2,4-disulfate) or piperazine-di-antimonyl tartrate at 0.7 to 2 mg/kg for 15 days to guinea pigs has been reported.

Lifetime oral exposure to potassium antimony tartrate (about 0.8 mg Sb/kg/day) in drinking water was without effect in mice, but 0.4 mg Sb/kg/day caused decreased longevity and altered blood levels of cholesterol and glucose in rats. Oral doses of 8 to 100 mg Sb/kg/day (as potassium antimony tartrate) for 4 months to 1 year did not cause decreased growth in rats or rabbits; however, histological changes such as congestion and altered fiber appearance in the heart, congestion with degeneration and polymorphonuclear leukocyte infiltration in the liver, and congestion with glomerulonephritis and tubular necrosis in the kidney were observed.

Although antimony may cross the placental barrier (see Section III.B), orally ingested antimony at doses of 190 mg Sb/kg/day did not interfere with pregnancy in dogs. Parenterally administered antimony (about 2.2 mg Sb/kg)

led to decreased fertility in rabbits and mice. No abnormalities were found in rat fetuses whose mothers were exposed to pentavalent antimonial drug RL-712. No adverse effects were found in ewes whose mothers were fed potassium antimony tartrate for 45 days or throughout gestation.

Various salts of antimony have been found to be mutagenic in various test systems. Antimony trichloride, antimony pentachloride, and antimony trioxide induced DNA damage in bacteria. Potassium antimony tartrate and sodium antimony tartrate induced chromosomal aberrations in human leukocytes. Piperazine antimony tartrate and potassium antimony tartrate induced chromosomal aberrations in bone marrow cells of rats.

Evidence shows that carcinogenicity of antimony is directly associated with the route of exposure. Antimony dust and ore, when inhaled, appears to be carcinogenic in both animals and humans. Primary lung tumors were observed with no evidence for systemic neoplasia. In contrast, no evidence of carcinogenicity was found in studies with two different strains of rats (Charles River CD and Long-Evans) in which exposure to antimony was via drinking water. However, these studies were not adequate tests for the carcinogenic potential of antimony in drinking water, since only one dose level was employed and an MTD was not demonstrated. Lifetime exposure of rats and mice to potassium antimony tartrate in drinking water at doses of 0.43 or 0.83 mg Sb/kg/day, respectively, did not result in increases in tumor frequencies.

VI. HEALTH EFFECTS IN HUMANS

A. CLINICAL CASE STUDIES

Cases of antimony toxicity resulting from oral ingestion are infrequent in humans. Kaplan and Korff (1936) briefly reviewed several reports of "food poisoning" that were traced to antimony extracted from enamel-coated vessels by acid contents (lemonade). Symptoms were not detailed, but acute attacks of vomiting occurred in at least one case. The amount of antimony ingested was not reported. Tests performed by the authors indicated that 0.5 to 2.6 mg of antimony could be extracted into 200 g of sauerkraut, an amount equal to about one-fourth of an emetic dose. It may be noted that antimony migrates only in traces from pottery into drinks (Zawadzka and Brzozowska, 1979). However, intoxication of antimony with contaminated drinks from vessels or tartar emetic is known (McCallum, 1977). The maximum contents of antimony in food tolerated by the U.S. FDA is 2 ppm (Spitz and Goudie, 1967).

Miller (1982) reported a case of antimony poisoning leading to the death of a patient (Oliver Goldsmith, a famous English author) suffering from headache, kidney trouble, and fever. The patient was administered two or three doses of James powder (each dose containing 66 mg of antimony) and consequently received a total of 132 to 198 mg of antimony (1 to 1.5 mg/kg of body weight). The treatment resulted in severe vomiting and diarrhea lasting for 18 hours and, finally, death.

Antimony compounds are used in human medicine for the treatment of various parasitic diseases such as schistosomiasis. These are generally organic antimonials and are administered parenterally, either intravenously or intramuscularly.

Jolliffe (1985) reported the effect of sodium stibogluconate ("Pentostam") given intravenously, for 10 days, in a standard daily dose of 600 mg Sb (V) to 16 British soldiers with cutaneous leishmaniasis. The treatment did not adversely affect either glomerular or renal functions. Stemmer (1976) noted that similar to arsenic compounds, the trivalent compounds of antimony are more toxic than pentavalent compounds.

Schroeder et al. (1946) studied the effect of trivalent and pentavalent antimony compounds on the electrocardiograms of human patients being treated for schistosomiasis with potassium antimony tartrate or sodium antimony bis(pyrocatechol-2,4-disulfonate) (Stibophen NF or Fuadin). Fuadin was given intramuscularly, and potassium antimony tartrate was given intravenously, daily or on alternate days, for about 1 month. Assuming an average body weight of 70 kg, average daily doses ranged from 0.24 to 0.89 mg Sb/kg/day. Examination of 315 electrocardiograms (EKGs) from 100 patients revealed the following alterations: increased P-wave amplitude in 11% of the patients; fusion of S-T segment and T-waves in 45% of the patients; decreased T-wave amplitude in 99% of the patients; and prolongation of the Q-T interval in 27% of the patients. The duration of the changes was variable but was noted up to 2 months after treatment ended in some cases. The authors concluded that these effects were not indicative of cardiac damage or serious impairment of cardiac function.

Rugemalila (1980) reported the incidence of two deaths due to parenteral antimony (astiban) intoxication. The first case involved a 4-year-old girl with a history of periodic fevers. She was administered (route not specified) 100 mg astiban (stibocaptate) for active schistosomiasis. This corresponds to a dose of about 2 mg Sb(III)/kg. Two weeks elapsed before she returned for a second dose, after which she developed severe vomiting and diarrhea. She then

become comatose, with dehydration and hepatosplenomegaly. Shortly thereafter, she developed fits and died. Analysis of cerebrospinal fluid showed decreased sugar levels, and postmortem examination showed marked hepatic microvacuolar steatosis. Death was attributed to hepatotoxicity. The second case involved a 70-year-old woman who was put on weekly injections of 320 mg astiban (about 2 mg Sb(III)/kg) to control hookworm. A few hours after receiving her second injection, she displayed breathlessness, coughing, and fainting. She was dyspneic and had low blood pressure, cardiomegaly, bilateral basal pulmonary crepitations, and hepatomegaly. Her condition deteriorated rapidly, and death ensued. Death was attributed to heart failure.

Christopherson (1921) described an 18-year-old male patient who developed skin complications during the course of treatment with intravenous injections of potassium antimony tartrate (87.5 g in 86 days). After an accumulated dose of 30 g, the patient developed leukoderma, a pigment disturbance that gives a piebald appearance to the skin. In addition, the man's skin became rough, dull, bumpy, and granular, resembling goose skin. This condition continued to exist 1 to 2 months after the end of treatment.

B. EPIDEMIOLOGICAL STUDIES

Several reports on health effects related to occupational exposure to antimony by inhalation have been reported. Oliver (1933) examined the health of six adult males who had worked in an antimony smelter for 2 to 13 years and received considerable exposure to antimony as evidenced by the presence of antimony in the feces (an average of 47.5 mg) but not in the urine. No signs of adverse effects were identified, including cardiac, kidney, or bladder effects, general health, and hematology.

Brieger et al. (1954) examined workmen in a plant where antimony trisulfide was used in the manufacture of grinding wheels. Antimony levels were as high as 5.5 mg/m^3 (equal to approximately 0.4 mg/kg antimony trisulfide). This study focused on cardiovascular status, since prior to the study there had been six sudden deaths in a group of 125 workers exposed to antimony for 8 months to 2 years. The deaths were suspected to be due to heart disease. In the workers studied, 14 of 113 had blood pressures that were >150/90 mmHg, and 37 of 75 showed significant changes in their EKGs, mostly the T-wave. Ulcers were detected in 7 of 111 exposed persons (63 per 1,000) as compared with 15 per 1,000 in the total plant population. No other disorders suspected of being related to antimony exposure were observed. Although use of Sb_2S_3 was discontinued, EKG changes persisted in 12 of 65 workers subsequently reexamined.

Chulay et al. (1985) studied EKG changes in 59 Kenyan patients treated with pentavalent antimony (sodium stibogluconate) for leishmaniasis. Dose-related increases in EKG abnormalities were found following 65 courses of antimony treatment. The incidences of EKG abnormalities were 22% (2/9 patients) at 10 mg Sb/kg/day; 52% (25/48 patients) at 20 to 30 mg Sb/kg/day; and 100% (8/8 patients) at 40 to 60 mg Sb/kg/day. Furthermore, the frequency of EKG abnormalities increased with the duration of the treatment. The abnormalities occurred in 41% (18/49) of the patients after 7 days, 67% (26/39) of the patients after 30 days, and 92% (11/12) of the patients after 60 days.

Belyaeva (1967) presented suggestive evidence of possible adverse effects of antimony in female workers employed in an antimony plant. When compared to female workers working under similar conditions but not exposed to antimony dust, the female workers in the antimony plant showed increased incidence of spontaneous abortions, premature births, and other gynecological problems.

Doll (1985) investigated the occupational causes of cancer. Mortality due to lung cancer was compared with mortality due to other causes in a British factory manufacturing antimony oxide. The compound was manufactured before World War II, but no records were available before 1961 either for dust measurements or for males who terminated employment. Antimony oxide dust has been greatly reduced since the 1960s. As shown in Table VI-1, an increase in lung cancer (SMR = 186) was observed for men first employed prior to 1961.

Potkonjak and Pavlovich (1983) reported clinical findings for 51 workers exposed to dust containing a mixture of antimony trioxide (up to 88%) and antimony pentoxide in an antimony smelting plant. Fifty-one male workers between the ages of 31 and 54, who had worked as smelters in the factory for 9 to 31 years (mean 17.91), were examined two to five times over a 25-year period. Characteristic changes observed in the smelters were described as a form of pneumoconiosis simplex or antimoniosis. The symptoms observed included chronic coughing, conjunctivitis, orange-colored staining of frontal tooth surface, chronic bronchitis, chronic emphysema, inactive tuberculosis, and pleural adhesions. "Antimony dermatitis" characterized by vesicular or pustular lesions was seen in more than half the exposed workers.

Kennedy (1966) measured antimony content in lung tissues obtained at autopsy or surgery from 24 patients with or without lung tumors. There was no correlation between antimony content and lung tumors.

C. HIGH-RISK POPULATIONS

No specific high-risk populations have been identified, although Davis (1975) suggested that bilharzial patients with overt skin, heart, renal, or hepatic disease or who are pregnant should not be treated with antimonials.

Table VI-1. Mortality of Males Employed in a Factory Manufacturing Antimony Oxide and Followed Through December 1981

Category of employees	No. of deaths: Observed	No. of deaths: Expected at local conurbation[a] rates	Standardized mortality ratio
Men first employed before 1961			
Lung cancer	31	16.7	186
Other causes	101	107.7	94
Men first employed January 1961 through December 1981			
Lung cancer	7	10.1	69
Other causes	62	84.0	74

[a] An aggregation of urban communities.

SOURCE: Adapted from Doll (1985).

D. SUMMARY

Only a few studies of antimony toxicity following oral exposure in humans were found. Most cases involved ingestion of food or liquid stored in antimony-containing enamel vessels, and the symptoms that followed were characteristic of gastrointestinal distress (nausea, vomiting). In one case, administration of 132 to 198 mg antimony led to severe vomiting, diarrhea, and finally death.

Inhalation of antimony due to occupational exposure is more common, and abnormal EKGs and increased ulcer frequency have been reported.

Parenteral administration of antimony compounds is used in the treatment of various parasitic diseases. Some cases of adverse response to such treatments have been noted, and reported effects included vomiting, diarrhea, liver dysfunction, and skin abnormalities.

Dose-related increases in EKG abnormalities were found in 59 Kenyan patients following 65 courses of antimony treatment. An increase in lung tissue concentration of antimony (280 ppb mg/kg compared with 32 and 19 ppb in controls) was found in 76 copper smelter workers at autopsy. Evidence suggestive of adverse reproductive effects, including spontaneous abortions and premature births, was reported in female workers employed in an antimony plant.

VII. MECHANISMS OF TOXICITY

A. ENZYME INHIBITION

Antimony, like other metal cations, interacts with proteins; therefore, most studies of the mechanism of antimony toxicity focus on antimony-induced inhibition of various enzyme activities.

Barron and Kalnitsky (1947) reported that 2×10^{-3} M Sb(III) (as sodium antimony biscatechol disulfonate) produced half-maximal inhibition of succinate oxidase (isolated from pigeon breast) *in vitro*, and that this could be reversed by 4×10^{-2} M glutathione.

Amer et al. (1967, 1969) studied the effect of antimony drugs on tryptophan metabolism in homogenates of mouse liver. The authors reported that kynureninase and kynurenine transaminase were both inhibited by the drugs in proportion to the amount of antimony added. Pyridoxal phosphate is a required cofactor for both these enzymes, and it appeared that antimony interacted with this cofactor in a way that inhibited enzyme activity.

Kelada et al. (1972) studied the effect of potassium antimony tartrate on tryptophan metabolism in children being treated for schistosomiasis. Eight children (5 to 12 years old, 21 to 35 kg) were given an oral dose of 0.5 g tryptophan, and the pattern of urinary metabolites was measured 24 hours later before and after treatment with potassium antimony tartrate. Treatment with 6 to 12 intravenous (iv) injections of potassium antimony tartrate (1 to 2 mg/kg) resulted in a pattern of urinary metabolites that indicated that tryptophan metabolism was inhibited. These *in vivo* results support the *in vitro* results of Amer et al. (1967, 1969).

B. ENZYME ACTIVATION

Drummond and Kappas (1981) studied the enhancement of heme degradation in rats treated with antimony compounds. Subcutaneous administration of $SbCl_3$ or $SbCl_5$ as single doses in the range of 3 to 30 mg Sb/kg resulted in a dose-dependent increase in the activity of heme oxygenase, the rate-limiting enzyme in the oxidative metabolism of heme to bile pigment. A maximum induction effect of heme oxygenase activity, 10-fold in the liver and 11-fold in the kidney, was observed with $SbCl_3$ at a dose of 15 mg Sb/kg. On the other hand, in animals dosed with $SbCl_5$, maximal increase of heme oxygenase activity was only 3-fold in the liver and 1.5-fold in the kidney at respective doses of 30 and 15 mg Sb/kg. Associated with the increase in heme oxygenase activity, renal and hepatic levels of cytochrome P-450, hepatic levels of microsomal heme, and aniline hydroxylase activity were decreased in rats dosed with $SbCl_3$ at 30 mg Sb/kg. These decreases were observed despite an increase in the activity of delta-aminolevulinate synthetase, the rate-limiting enzyme in the synthesis of heme. Subcutaneous administration of trivalent antimonium, as the parasiticidal drugs antimony potassium tartrate and antimony sodium dimercapto-succinate, at a dose of 10 mg Sb/kg, also resulted in a significant increase in heme oxygenase activity in the liver. No such increase in enzyme activity was observed when sodium stibogluconate, containing pentavalent antimony, was administered at a dose of 10 mg Sb/kg.

C. INTERACTIONS

A number of reports indicate that the effects of antimony are reduced by various sulfhydryl reagents. For example, Girgis et al. (1970) reported that treatment of dogs with penicillamine (3-mercaptovaline) reduced the changes in the electrocardiogram caused by potassium antimony tartrate. Both compounds

were administered intravenously. The authors suggested that the sulfhydryl group of penicillamine competitively inhibits antimony binding to intracellular sulfhydryl-containing enzymes.

Antimony has an inhibitory effect on the tryptophan-niacin pathway, specifically inhibiting kynureninase and kynurenine transaminase (Amer et al., 1967, 1969). Kelada et al. (1972) studied the effects of potassium antimony tartrate (given intravenously) and 2,3-dimercaptopropanol (given intramuscularly) on the tryptophan-niacin pathway in 5- to 12-year-old children. The authors found that 2,3-dimercaptopropanol, a metal chelator, prevented antimony inhibition of the tryptophan-niacin pathway.

Saleh and Khayyal (1976) used cysteine as an adjunct to potassium antimony tartrate (both given intraperitoneally) and found that this compound reduced the acute toxicity of antimony in albino mice (strain not indicated) (Figure VII-1). The LD_{50} of antimony was raised from 33 to 47 mg/kg. Liver function tests in rabbits were analyzed after treatment with parenteral potassium antimony tartrate (PAT) and cysteine. The tests included (1) serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT); (2) alkaline phosphatase (AP); (3) thymol turbidity and flocculation; (4) icterus index; and (5) serum lipoproteins. Rabbits were injected with PAT at 4 mg/kg daily for 5 days either alone or in addition to a separate injection of 12 mg/kg cysteine. One group of rabbits received cysteine (12 mg/kg) alone and another group of untreated rabbits was maintained as controls. There was no significant difference in icterus index and thymol turbidity test between PAT-treated rabbits with or without cysteine, but there was significant reduction of SGOT, SGPT, and AP with cysteine + PAT treatment ($p < 0.05$) (Figure VII-2).

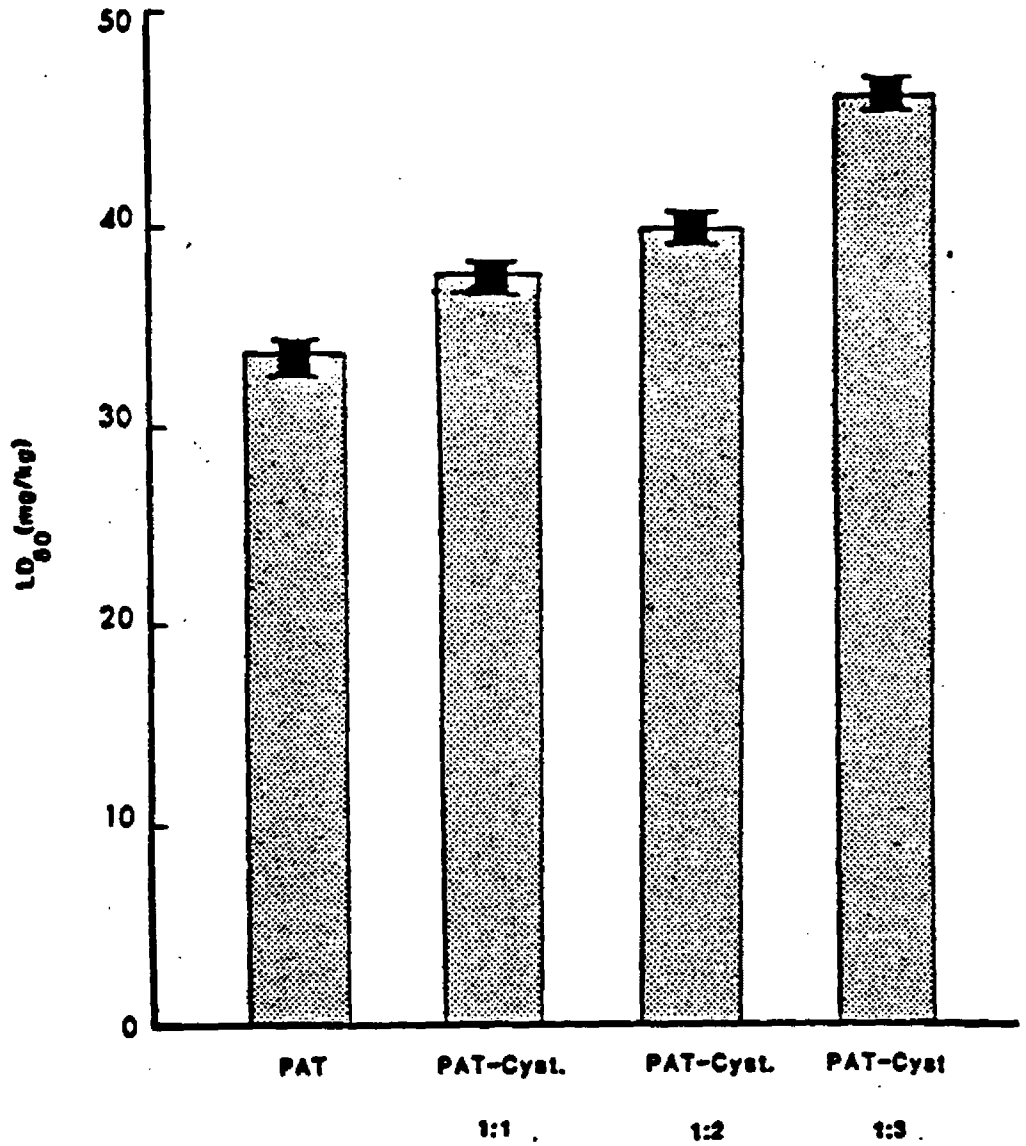


Figure VII-1. Effect of cysteine on the LD_{50} of potassium antimony tartrate (PAT) in mice.

SOURCE: Adapted from Saleh and Khayyal (1976).

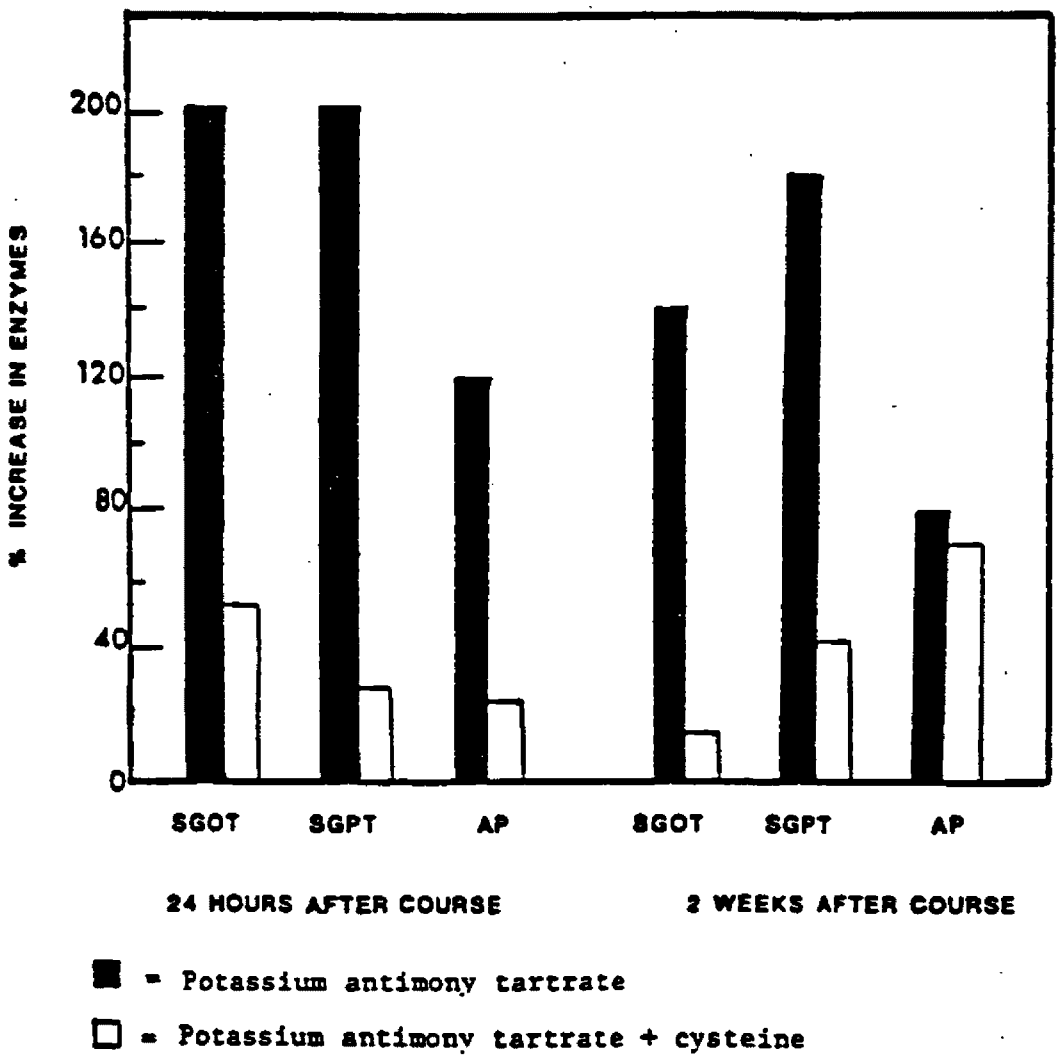


Figure VII-2. Effect of cysteine on serum enzymes in rabbits treated with potassium antimony tartrate.

SOURCE: Adapted from Saleh and Khayyal (1976).

The results suggest that the thiol groups of cysteine bind with antimony and prevent its binding with intracellular enzymes. However, because both cysteine and APT were administered via the same route (ip), there is a possibility of interaction of the two chemicals prior to absorption into the blood stream. This interaction could essentially decrease the amount of antimony available for absorption from the peritoneal cavity.

Moxon et al. (1947) found that antimony was partially effective in preventing selenium toxicity. Groups of young rats (two males and three females, age and strain not given) were fed diets containing neither selenium nor antimony (control), selenium alone (12 ppm), or selenium (12 ppm) plus antimony (12 ppm Sb, as $SbCl_3$), and body weights were measured for 90 days. Selenium alone caused a marked decrease in the rate of weight gain, and this was partially reversed by inclusion of antimony in the diet. The effect of antimony alone was not investigated.

Westrick (1953) studied the interaction between antimony and the thyroid hormone in Sprague-Dawley rats. Animals receiving subcutaneous injections of thyroxin (1 mg/kg/day) showed decreased weight gains relative to controls after 25 to 50 days of treatment. Feeding of 2% Sb_2O_3 in the diet did not have an effect on weight gain in animals not treated with thyroxin but caused dramatic weight loss in animals receiving thyroxin (Figure VII-3). Using a mean body weight of 0.18 kg (the mean of reported initial and final weights) and assuming average food consumption of 12 g/day (Arrington, 1972), this corresponds to an average daily dose of 1,114 mg Sb/kg/day. The author concluded that antimony enhanced the action of thyroxin in extrathyroidal tissues.

Baetjer (1969) injected (iv or ip) 10 or 15 mg potassium antimony tartrate/kg into dehydrated or hyperthermal mice and rats (no species, weight, or

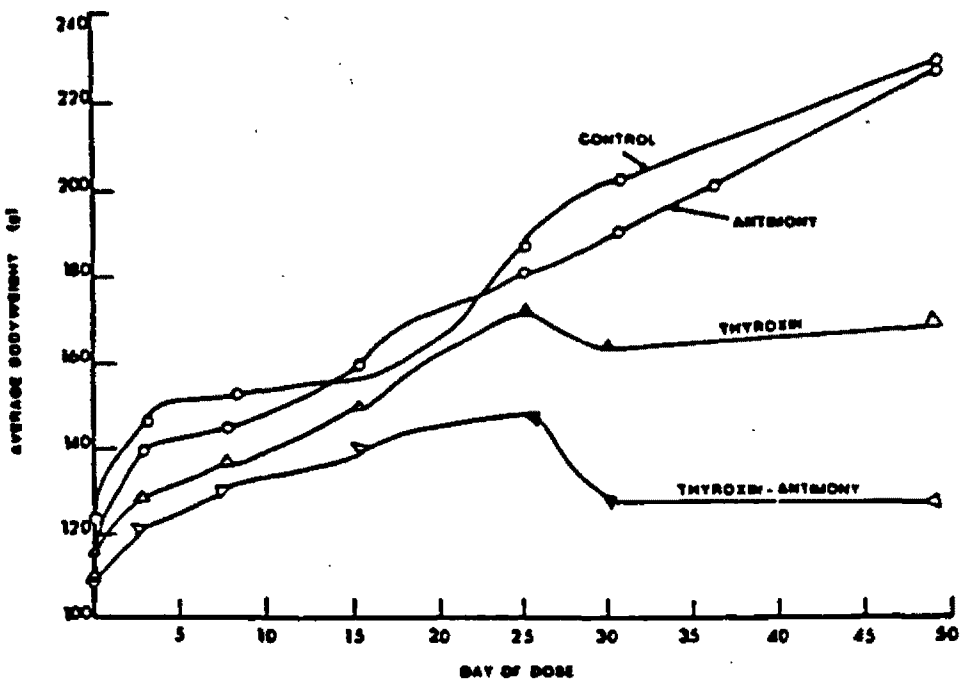


Figure VII-3. Average body weights of rats treated with dietary antimony, with and without parenteral thyroxin.

SOURCE: Adapted from Westrick (1953).

age given). Dehydration was created by water deprivation 24 to 72 hours before dosing or by substitution of 2% saline for drinking water 1 to 3 weeks prior to antimony dosing. Hyperthermia was created by exposure to a temperature of 34.4°C for 1 week following antimony dosing. Dehydration caused an increase in mortality and decreased survival time in both rats and mice (Table VII-1). Exposure of rats and mice to a high temperature increased antimony-induced mortality and decreased survival time (Table VII-2). The effect of dehydration or hyperthemia alone (no antimony exposure) was not reported. The author suggested that data support the theory that hyperthermia or dehydration may contribute to sensitivity to antimony toxicity.

D. SUMMARY

Antimony is thought to exert its toxic effects by interacting with intracellular enzymes or cofactors. A number of sulfhydryl-containing compounds reduce the toxic effects of antimony, suggesting that it may bind to cellular sulfhydryl groups. Antimony has been reported to increase the activity of heme oxygenase, increase the action of the thyroid hormone, and to decrease the toxicity of selenium, but the mechanism of these effects is not known.

Table VII-1. Effect of Potassium Antimony Tartrate and Dehydration on Mortality in Rats and Mice

Species	Dose (mg Sb/kg)	Route of injection	Mortality		Probability ($p \leq$)
			Sb	Sb + dehydration	
Rat	10	iv	11.1 (19)[a]	100.0 (10)	0.003
	10	iv	50.0 (10)	100.0 (10)	0.032
	10	iv	5.3 (19)	36.8 (19)	0.21
	15	iv	84.6 (39)	100.0 (41)	0.012
	15	iv	100.0 (12)	100.0 (12)	NS[b]
	15	iv	100.0 (9)	100.0 (13)	NS
	15	iv	60.0 (20)	100.0 (20)	0.003
Mouse	15	iv	13.3 (30)	73.3 (30)	<0.001
	15	iv	20.0 (15)	22.2 (18)	NS
	15	iv	10.0 (20)	80.0 (20)	<0.001
	15	iv	20.0 (15)	66.7 (9)	0.021
	15	iv	13.3 (15)	21.4 (14)	NS
	15	ip	--[c]	50.0 (10)	--
	15	ip	20.0 (5)	88.9 (9)	0.046
	15	ip	--	0.0 (5)	--

[a]Values in parentheses denote sample size.
[b]NS = Not significant.
[c]No data were reported.

SOURCE: Adapted from Baetjer (1969).

Table VII-2. Effect of Potassium Antimony Tartrate and Environmental Temperature on Mortality in Rats and Mice

Species	Sex	Mortality (%)		Probability ($p \leq$)
		Normothermia	Hyperthermia	
Rat	Male[a]	35.7 (14)[b]	100.0 (14)	0.01
	Female[c]	0.0 (6)	20.0 (5)	NS[d]
Mouse	Male[a]	25.0 (24)	87.5 (24)	0.01

[a]Administered by intravenous injection.
[b]Value in parentheses is sample size.
[c]Administered by intraperitoneal injection.
[d]NS = Not significant.

SOURCE: Adapted from Baetjer (1969).

VIII. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

The quantification of toxicological effects of a chemical consists of an assessment of noncarcinogenic and carcinogenic effects. Chemicals that do not produce carcinogenic effects are believed to have a threshold dose below which no adverse, noncarcinogenic health effects occur, whereas carcinogens are assumed to act without a threshold.

A. PROCEDURES FOR QUANTIFICATION OF TOXICOLOGICAL EFFECTS

1. Noncarcinogenic Effects

In the quantification of noncarcinogenic effects, a Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI), is calculated. The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious health effects, even if exposure occurs over a lifetime. The RfD is derived from a No-Observed-Adverse-Effect Level (NOAEL) or Lowest-Observed-Adverse-Effect Level (LOAEL), identified from a subchronic or chronic study, and divided by an uncertainty factor (UF). The RfD is calculated as follows:

$$\text{RfD} = \frac{\text{(NOAEL or LOAEL)}}{\text{Uncertainty factor}} = \_\_\_ \text{ mg/kg bw/day}$$

Selection of the uncertainty factor to be employed in the calculation of the RfD is based on professional judgment while considering the entire data base of toxicological effects for the chemical. To ensure that uncertainty factors are selected and applied in a consistent manner, the Office of Drinking Water (ODW) employs a modification to the guidelines proposed by the National Academy of Sciences (NAS, 1977, 1980), as follows:

- An uncertainty factor of 10 is generally used when good chronic or subchronic human exposure data identifying a NOAEL are available and are supported by good chronic or subchronic toxicity data in other species.

- An uncertainty factor of 100 is generally used when good chronic toxicity data identifying a NOAEL are available for one or more animal species (and human data are not available), or when good chronic or subchronic toxicity data identifying a LOAEL in humans are available.

- An uncertainty factor of 1,000 is generally used when limited or incomplete chronic or subchronic toxicity data are available, or when good chronic or subchronic toxicity data identifying a LOAEL, but not a NOAEL, for one or more animal species are available.

The uncertainty factor used for a specific risk assessment is based principally on scientific judgment, rather than scientific fact, and accounts for possible intra- and interspecies differences. Additional considerations not incorporated in the NAS/ODW guidelines for selection of an uncertainty factor include the use of a less-than-lifetime study for deriving an RfD, the significance of the adverse health effect, and the counterbalancing of beneficial effects.

From the RfD, a Drinking Water Equivalent Level (DWEL) can be calculated. The DWEL represents a medium-specific (i.e., drinking water) lifetime exposure at which adverse, noncarcinogenic health effects are not expected to occur. The DWEL assumes 100% exposure from drinking water. The DWEL provides the noncarcinogenic health effects basis for establishing a drinking water standard. For ingestion data, the DWEL is derived as follows:

$$DWEL = \frac{RfD \times (\text{body weight in kg})}{\text{Drinking water volume in L/day}} = \_\_\_\_ \text{ mg/L}$$

where:

Body weight = assumed to be 70 kg for an adult.

Drinking water volume = assumed to be 2 L per day for an adult.

In addition to the RfD and the DWEL, Health Advisories (HAs) for exposures of shorter duration (One-day, Ten-day, and Longer-term HAs) are determined. The HA values are used as informal guidance to municipalities and other organizations when emergency spills or contamination situations occur. The HAs are calculated using a similar equation to the RfD and DWEL; however, the NOAELs or LOAELs are identified from acute or subchronic studies. The HAs are derived as follows:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (bw)}{(\_\_\_ \text{ L/day}) \times (UF)} = \_\_\_ \text{ mg/L} \quad (\_\_\_ \text{ ug/L})$$

Using the above equation, the following drinking water HAs are developed for noncarcinogenic effects:

1. One-day HA for a 10-kg child ingesting 1 L water per day.
2. Ten-day HA for a 10-kg child ingesting 1 L water per day.
3. Longer-term HA for a 10-kg child ingesting 1 L water per day.
4. Longer-term HA for a 70-kg adult ingesting 2 L water per day.

The One-day HA, calculated for a 10-kg child, assumes a single acute exposure to the chemical and is generally derived from a study of less than 7 days' duration. The Ten-day HA assumes a limited exposure period of 1 to 2 weeks and is generally derived from a study of less than 30 days' duration. The Longer-term HA is calculated for both a 10-kg child and a 70-kg adult and assumes an

exposure period of approximately 7 years (or 10% of an individual's lifetime). The Longer-term HA is generally derived from a study of subchronic duration (exposure for 10% of an animal's lifetime).

2. Carcinogenic Effects

The EPA categorizes the carcinogenic potential of a chemical, based on the overall weight of evidence, according to the following scheme:

- Group A: Known Human Carcinogen. Sufficient evidence exists from epidemiology studies to support a causal association between exposure to the chemical and human cancer.
- Group B: Probable Human Carcinogen. Sufficient evidence of carcinogenicity in animals with limited (Group B1) or inadequate (Group B2) evidence in humans.
- Group C: Possible Human Carcinogen. Limited evidence of carcinogenicity in animals in the absence of human data.
- Group D: Not Classified as to Human Carcinogenicity. Inadequate human and animal evidence of carcinogenicity or for which no data are available.
- Group E: Evidence of Noncarcinogenicity for Humans. No evidence of carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies.

If toxicological evidence leads to the classification of the contaminant as a known, probable, or possible human carcinogen, mathematical models are

used to calculate the estimate of excess cancer risk associated with the ingestion of the contaminant in drinking water. The data used in these estimates usually come from lifetime exposure studies in animals. To predict the risk for humans from animal data, animal doses must be converted to equivalent human doses. This conversion includes correction for noncontinuous exposure, less-than-lifetime studies, and for differences in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average adult human body weight is 70 kg and that the average water consumption of an adult human is 2 liters of water per day.

For contaminants with a carcinogenic potential, chemical levels are correlated with a carcinogenic risk estimate by employing a cancer potency (unit risk) value together with the assumption for lifetime exposure via ingestion of water. The cancer unit risk is usually derived from a linearized multistage model, with a 95% upper confidence limit providing a low-dose estimate; that is, the true risk to humans, while not identifiable, is not likely to exceed the upper limit estimate and, in fact, may be lower. Excess cancer risk estimates may also be calculated using other models such as the one-hit, Weibull, logit, and probit. There is little basis in the current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than any others. Because each model is based on differing assumptions, the estimates that were derived for each model can differ by several orders of magnitude.

The scientific data base used to calculate and support the setting of cancer risk rate levels has an inherent uncertainty due to the systematic and random errors in scientific measurement. In most cases, only studies using

experimental animals have been performed. Thus, there is uncertainty when the data are extrapolated to humans. When developing cancer risk rate levels, several other areas of uncertainty exist, such as the incomplete knowledge concerning the health effects of contaminants in drinking water; the impact of the experimental animal's age, sex, and species; the nature of the target organ system(s) examined; and the actual rate of exposure of the internal targets in experimental animals or humans. Dose-response data usually are available only for high levels of exposure, not for the lower levels of exposure closer to where a standard may be set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

B. QUANTIFICATION OF NONCARCINOGENIC EFFECTS FOR ANTIMONY

1. One-day Health Advisory

No appropriate studies were found to be suitable for calculation of a One-day HA for antimony. The results from Flury (1927) were considered in developing a One-day HA for antimony. Flury (1927) indicated that nausea and vomiting occurred in cats and dogs at doses of 4 to 12 mg Sb/kg and that No-Observed-Adverse-Effect Levels (NOAELs) occurred at 2.6 to 6.0 in cats and dogs. However, these studies were judged inappropriate due to lack of study details and small number of animals per test dose. Therefore, in the absence of a more suitable study, it is recommended that the DWEL of 15 ug/L be used as a conservative estimate of the One-day HA for a 10-kg child.

2. Ten-day Health Advisory

Table VIII-1 summarizes the studies considered for calculation of the Ten-day HA for antimony. None of these studies were found to be suitable

Table VIII-1. Summary of Candidate Studies for Derivation of the Ten-day Health Advisory for Antimony

Reference	Species	Route	Exposure duration	Endpoint	NOAEL (mg Sb/kg/day)	LOAEL (mg Sb/kg/day)
Pribyl (1927)	Rabbit	Oral in milk	7-22 days	Histopathology: liver, kidney, intestine	--	5.6
Westrick (1953)	Rat	Diet	7 weeks	Body weight, oxygen consumption, hypermetabolism	--	10.9
Bomhard et al. (1982)	Rat	Diet	3 months	Growth, hematology, organ weight	>10	--
James et al. (1966)	Sheep	Oral	45 days	Hematology, mineral deposition in tissues	>2	--

for calculation of the ten-day HA. The study by Peribyl (1927) was not selected because it appeared outdated and offered very little details upon which a confident analysis could be made. The study by Westrick (1953) was not chosen, because the duration was excessive (7 weeks) and no histopathological examination of tissues was performed. In addition, the LOAEL was higher than that found in the Pribyl (1927) study. The study by Bomhard et al. (1982) was not selected, since the chemical given was an insoluble complex of several metals. The study by James et al. (1966) was not selected because the dose tested was not high enough to elicit a toxic response. In absence of appropriate data, it is recommended that the DWEL of 15 ug/L be used as a conservative estimate of the Ten-day HA.

3. Longer-term Health Advisory

Table VIII-2 summarizes the studies considered for calculation of the Longer-term HA values for antimony. None of the studies was found suitable for calculation of the Longer-term HA values because a good estimate of the NOAEL or LOAEL could not be obtained. The study by Westrick (1953) was not chosen, because no histological examination of the tissues was performed, the only selected dose (1,114 mg Sb/kg/day) was too high to permit calculation of a LOAEL, and the period of exposure (7 weeks) was too short. The studies by Bomhard et al. (1982) and James et al. (1966) were not selected because the doses studied were not high enough to elicit a toxic response. Additionally, in the Bomhard study the chemical administered was an insoluble complex of

Table VIII-2. Summary of Candidate Studies for Derivation of the Longer-term Health Advisory for Antimony

Reference	Species	Route	Exposure duration	Endpoint	NOAEL (mg Sb/kg/day)	LOAEL (mg Sb/kg/day)
Westrick (1953)	Rat	Diet	7 weeks	Body weight, oxygen consumption, hypermetabolism, organ weight	--	<1114
Bomhard et al. (1982)	Rat	Diet	3 months	Growth, hematology, organ weight	>10	--
James et al. (1966)	Sheep	Oral	45 days	Hematology, mineral deposition in tissues	>2	--
Bradley and Fredrick (1941)	Rat	Oral	6, 7-1/2, 12 months	Growth rate, blood count, gross pathology	--	--
Flury (1927)	Rat	Diet	107, 131 days	Growth	>1.5	--

several metals. The studies by Bradley and Fredrick (1941) were not selected, because in two studies only one dose was used, and in the third study continually increasing doses were used for the first 6 months. Neither a NOAEL or LOAEL was identified in these studies. The studies by Flury (1927) were not selected because very few animals were used per dose group and because most of the studies involved continually increasing doses of chemical. In the absence of a suitable study for calculation of the Longer-term HA, it is recommended that the DWEL for antimony of 15 ug/L be taken as an appropriate estimate of the Longer-term HA value for adults. It can be assumed that the DWEL value will more than adequately protect both adults and children over long-term exposures (6 to 12 months), since the RfD and DWEL values were based on a lifetime study in rodents and a large safety factor (1000) was incorporated into the derivation.

4. Reference Dose and Drinking Water Equivalent Level

Table VIII-3 summarizes the studies considered for derivation of the RfD and DWEL for antimony.

The study by Schroeder et al. (1970) has been selected to serve as the basis for calculation of the RfD and DWEL because it involved lifetime exposure of rats to potassium antimony tartrate (the most toxic of the common antimony compounds) given in drinking water. This study identified a LOAEL of 0.43 mg/kg/day on the basis of decreased longevity and altered blood levels of glucose and cholesterol. The lifetime study in mice by Schroeder et al. (1968) has not been selected because the LOAEL identified (0.8 mg Sb/kg/day) is based on a single parameter - namely decreased body weight of females after 12 months of antimony administration. Moreover, only a single dose was used. Antimony did not significantly suppress the growth of male mice except after 18 months

Table VIII-3. Summary of Candidate Studies for Derivation of the Drinking Water Equivalent Level for Antimony

References	Species	Route	Exposure duration	Endpoint	NOAEL (mg Sb/kg/day)	LOAEL (mg Sb/kg/day)
Schroeder et al. (1968)	Mouse	Drinking water	Lifetime	Body weight, liver histology	--	0.83
Schroeder et al. (1970)	Rat	Drinking water	Lifetime	Longevity, blood analysis	--	0.43

of antimony administration. No histopathological changes were observed in either sex.

Using this study, the DWEL is derived as follows:

Step 1: Determination of Reference Dose (RfD)

$$RfD = \frac{(.43 \text{ mg/kg/day})}{(1{,}000)} = 0.00043 \text{ mg/kg/day } (0.4 \text{ ug/kg/day})$$

where:

0.43 mg/kg/day = LOAEL, based on decreased longevity and altered blood glucose and cholesterol in rats exposed to potassium antimony tartrate in drinking water for a lifetime (Schroeder et al., 1970).

70 kg = assumed weight of adult.

1,000 = uncertainty factor. This uncertainty factor was chosen in accordance with ODW/NAS guidelines for use when a LOAEL from an animal study is employed.

Step 2: Determination of Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.00043 \text{ mg/kg/day})(70 \text{ kg})}{2 \text{ L/day}} = 0.015 \text{ mg/L } (15 \text{ ug/L})$$

where:

0.00043 mg/kg/day = RfD.

70 kg = assumed weight of adult.

2 L/day = assumed water consumption by 70-kg adult.

C. QUANTIFICATION OF CARCINOGENIC EFFECTS FOR ANTIMONY

Table VIII-4 summarizes the studies considered for calculation of carcinogenic risk estimates.

Table VIII-4. Summary of Candidate Studies for Calculation of Carcinogenic Risk Estimates

References	Species	Route	Exposure/study duration	Result
Schroeder et al. (1968)	Mouse	Drinking water	Lifetime	At a daily dose of 0.83 mg Sb/kg/day, 18.8% mice developed tumors (34.8% control).
Schroeder et al. (1970)	Rat	Drinking water	Lifetime	At a daily dose of 0.43 mg Sb/kg/day, no significant effect of antimony on tumor frequency was observed.
Watt (1983)	Rat	Inhalation	1 year/ 2 years	At a daily dose of 4.2 mg Sb/kg/day, female rats developed scirrhous carcinomas, squamous cell carcinomas, or bronchiolar adenomas.
Groth et al. (1986)	Rat	Inhalation	52 weeks/ 72 weeks	At levels close to threshold limit values, the rats developed primary lung neoplasms.

The evidence regarding the potential carcinogenicity of antimony when ingested in drinking water is inconclusive. This is based on the lack of carcinogenicity in two studies in which antimony was administered in drinking water to two strains of rats. These studies, however, are judged inadequate in design, since only one dose level was utilized and an MTD level may not have been achieved. In contrast, studies in which antimony dusts were inhaled by rats revealed primary lung neoplasia. Since no systemic neoplasia was evident and no absorption data were presented, these data cannot be utilized in assessing the potential carcinogenicity of a soluble form of antimony in drinking water. It should be noted that some evidence exists to indicate that workers inhaling antimony dust may also be at increased risk for lung tumors. The evidence in humans, however, is inadequate. On this basis, antimony in drinking water is categorized in Group D, not classified as to human carcinogenicity; thus, no quantification of carcinogenicity has been performed.

D. SUMMARY

Table VIII-5 summarizes HA and DWEL values (calculated on the basis of noncarcinogenic endpoints). Excess cancer risks were not estimated because there is no evidence that orally ingested antimony is carcinogenic in animals.

Table VIII-5. Summary of Quantification of Toxicological Effects for Antimony

Value	Drinking water Concentration (ug/L)	Reference
One-day HA for 10-kg child	--[a]	--
Ten-day Ha for 10-kg child	--[a]	--
Longer-term HA for 10-kg child	--[a]	--
Longer-term HA for 70-kg adult	--[a]	--
DWEL (70-kg adult)	15	Schroeder et al. (1970)
Excess cancer risk (10^{-6})	--	--

[a] It is recommended that the DWEL value be used as a conservative estimate for the one-day, ten-day and longer-term health advisory values.

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